MALATTIA NON METASTATICA

Principali Novità HER2+/TN

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Disclosures and potential conflicts of interest

- **Consulting/Advisor:** Roche, AstraZeneca, Lilly, GSK, Novartis, Pfizer
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- **Travel, accommodation, expenses:** Roche, AstraZeneca, Lilly, GSK, Novartis, Celgene, Pfizer

Early-stage TNBC

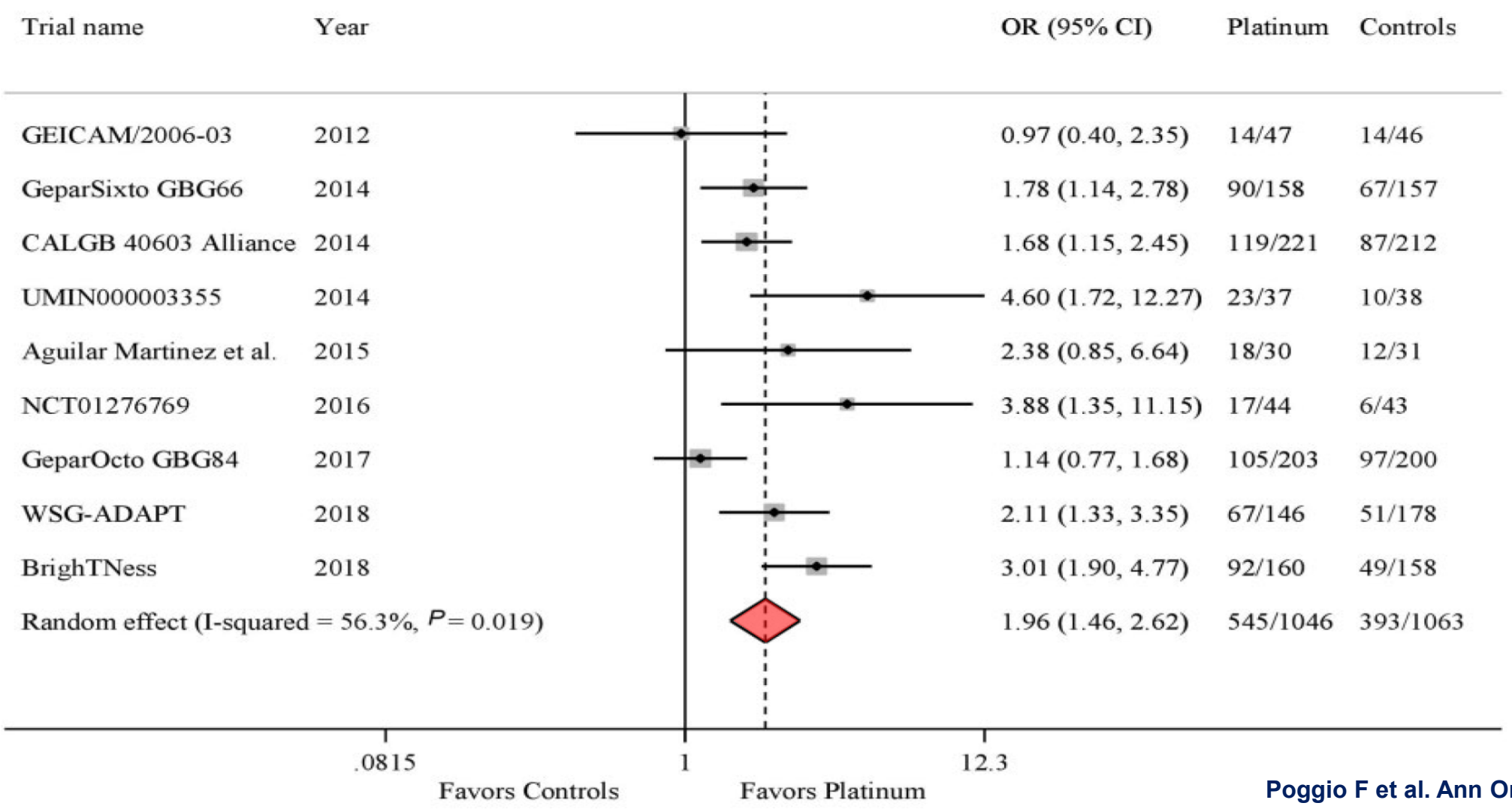
- Platinum agents
- Immunotherapy
- PARP inhibitors

Improving outcomes of early stage TNBC

"platinum or not platinum"

Neoadjuvant Platinum Trials

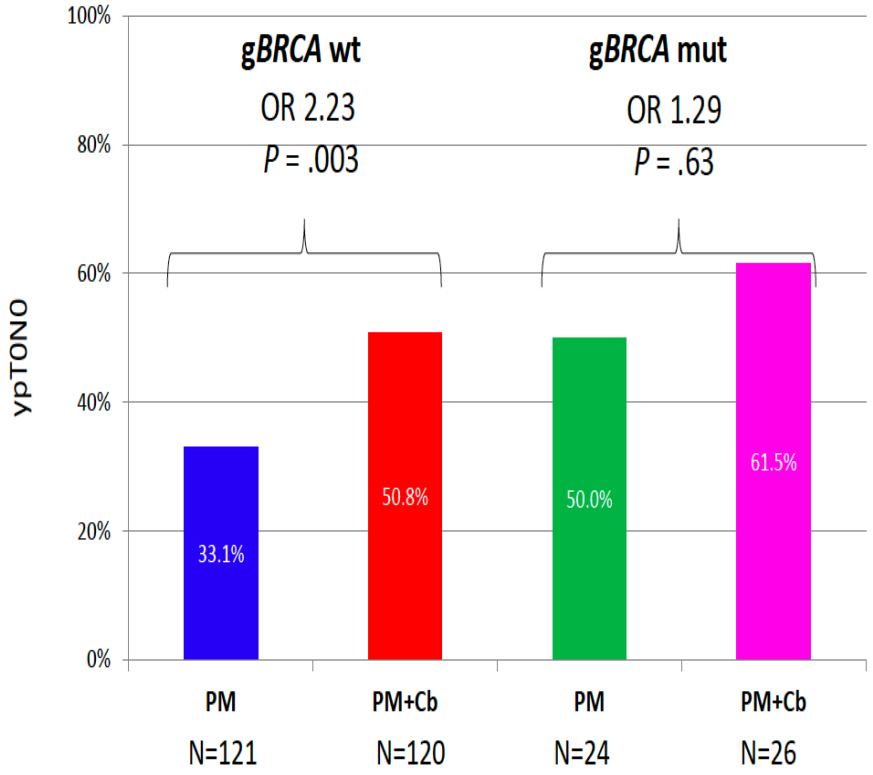
Metanalysis of pCR rates



Poggio F et al. Ann Oncol 2018

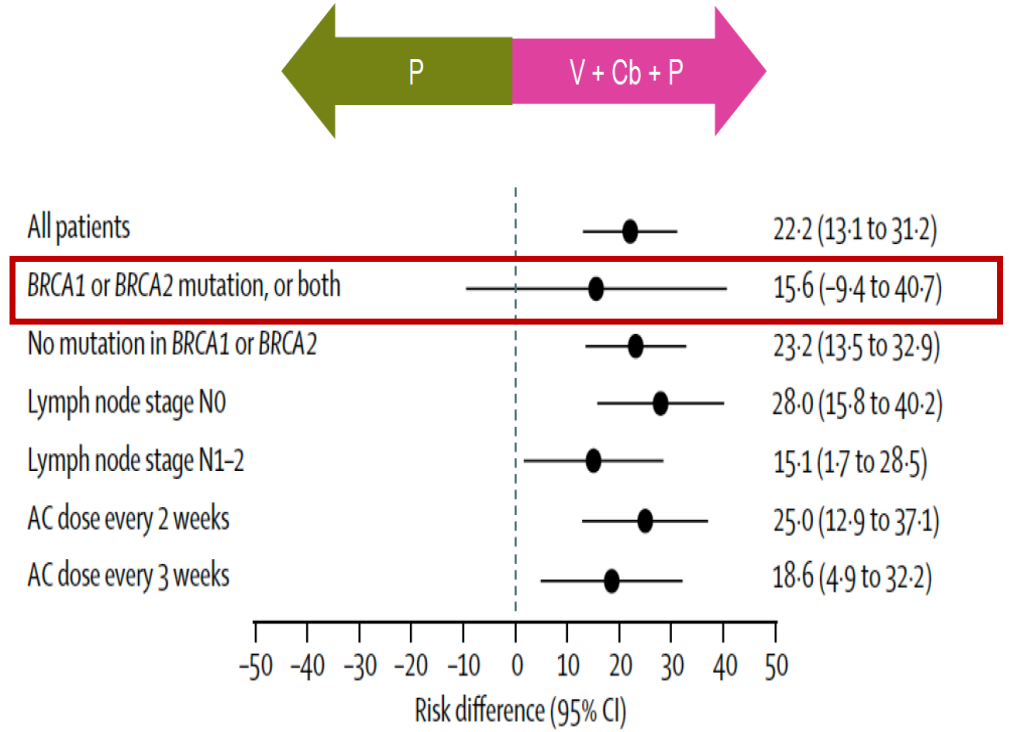
pCR rates by g*BRCA* status

GeparSixto



Haenen E et al. Jama Oncol 2017

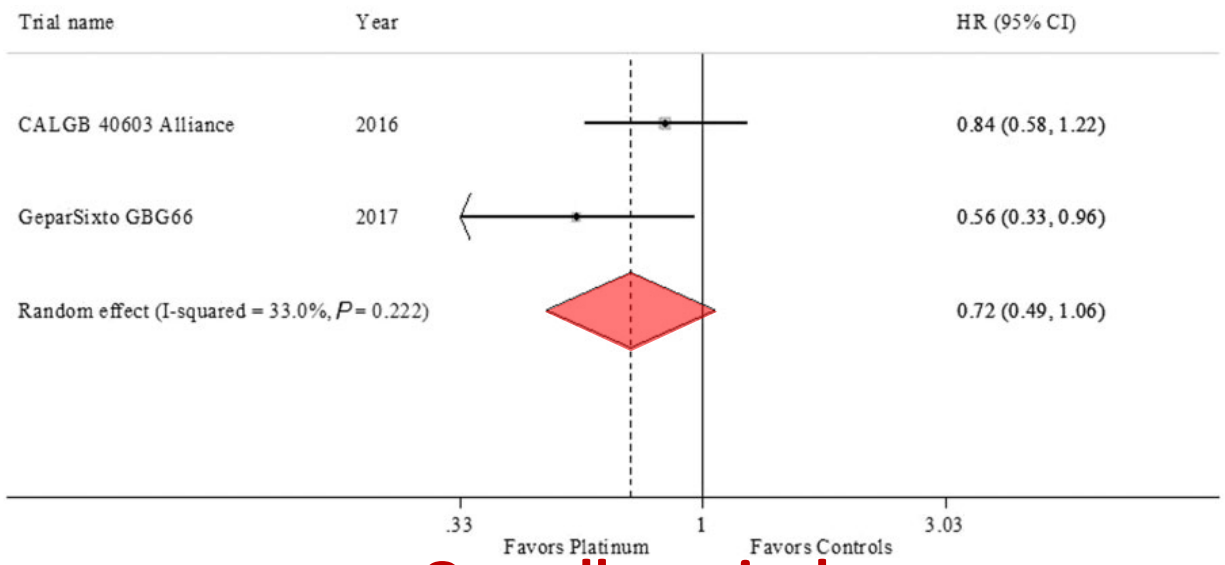
Brightness



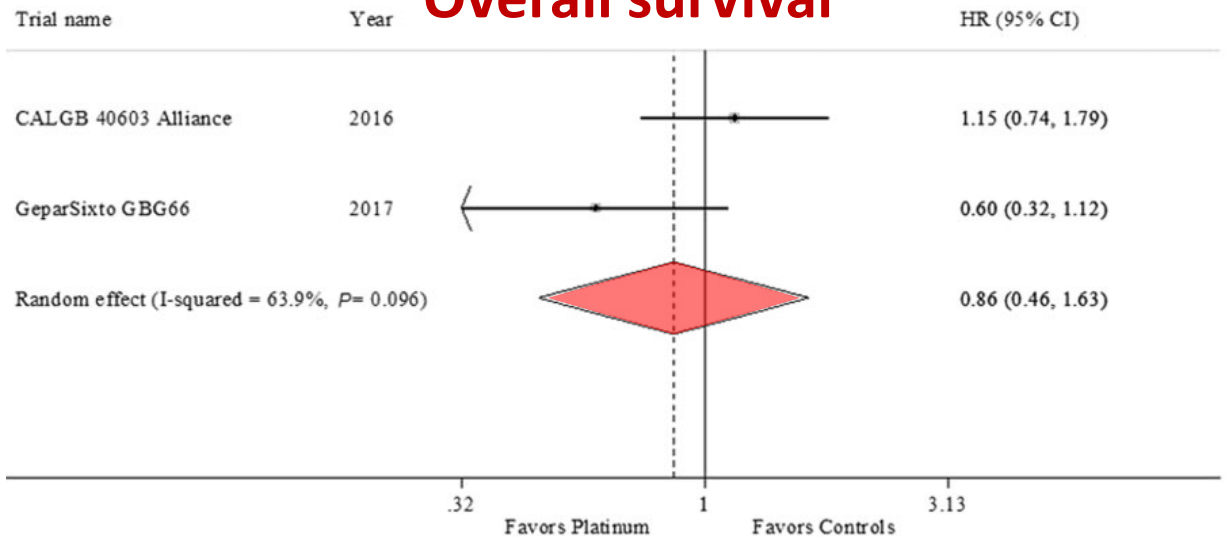
Loibl S et al. Lancet Oncol 2018

Neoadjuvant Platinum Trials

Event-free survival



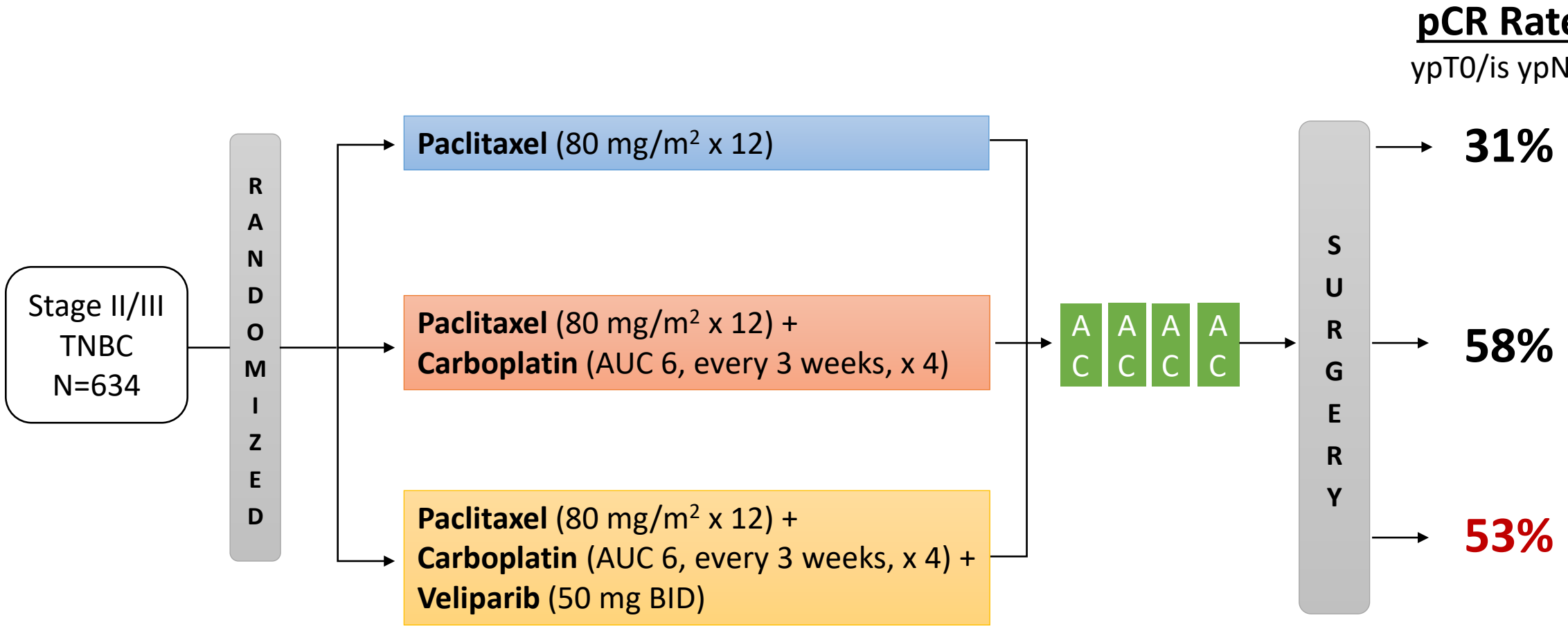
Overall survival



Adverse Events

Poggio F et al. Ann Oncol 2018

BrighTNess: Addition of carboplatin ± veliparib to standard neoadjuvant chemotherapy in TNBC

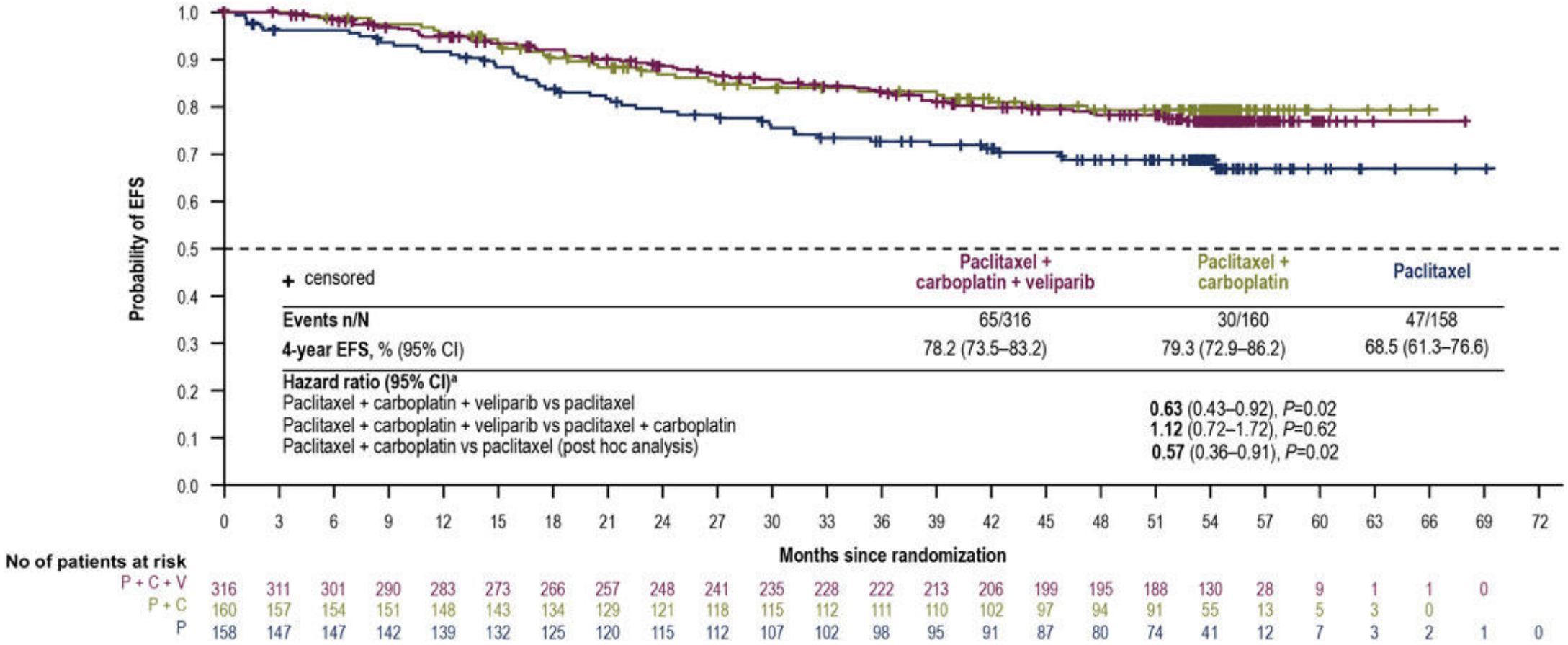


- 93 patients (15%) gBRCA+; no difference due to BRCA status

Loibl S et al., Lancet Oncol 2018

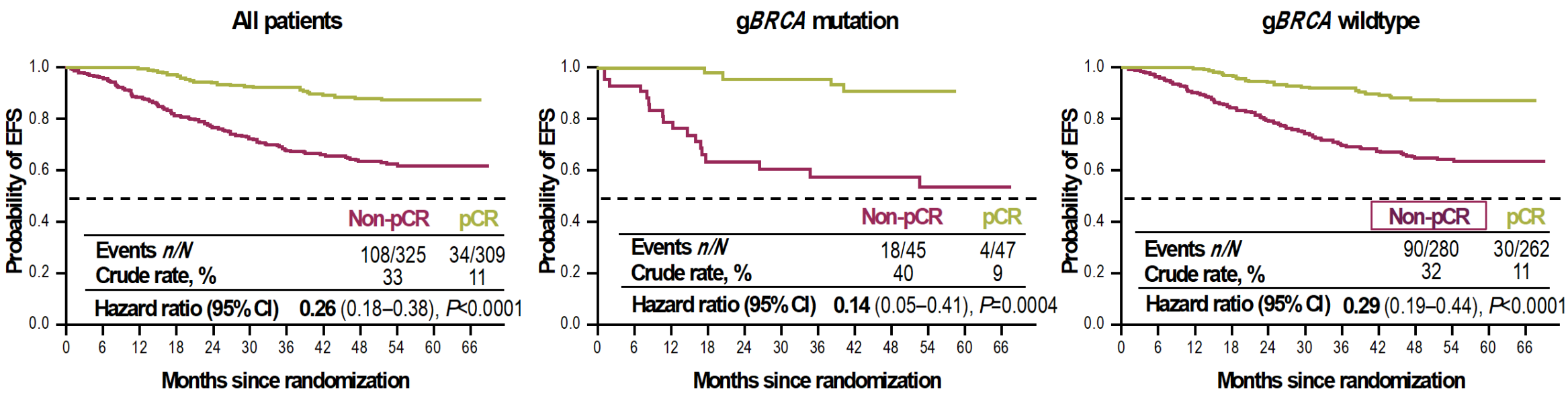
BrighTNess: The addition of carboplatin to standard neoadjuvant chemotherapy improves EFS in TNBC

Median follow-up of 4.5 years



Loibl S et al., ESMO 2021

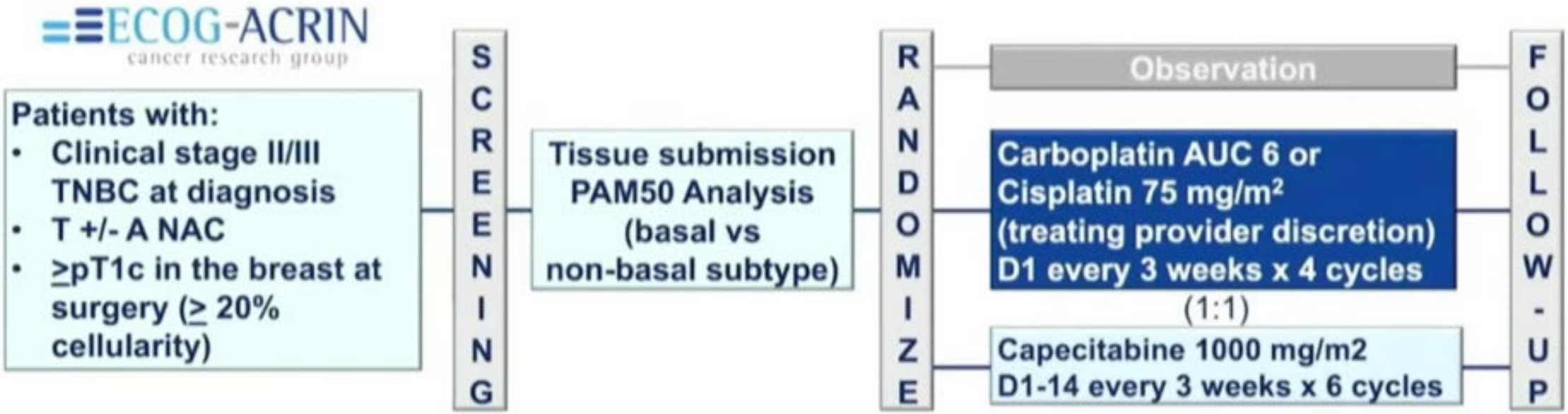
BrighTNess: EFS by pCR in all patients and subgroups by g*BRCA* status



Loibl S et al., ESMO 2021

Treatment strategies for early stage TNBC

EA1131: Does adjuvant platinum improve iDFS in basal TNBC?



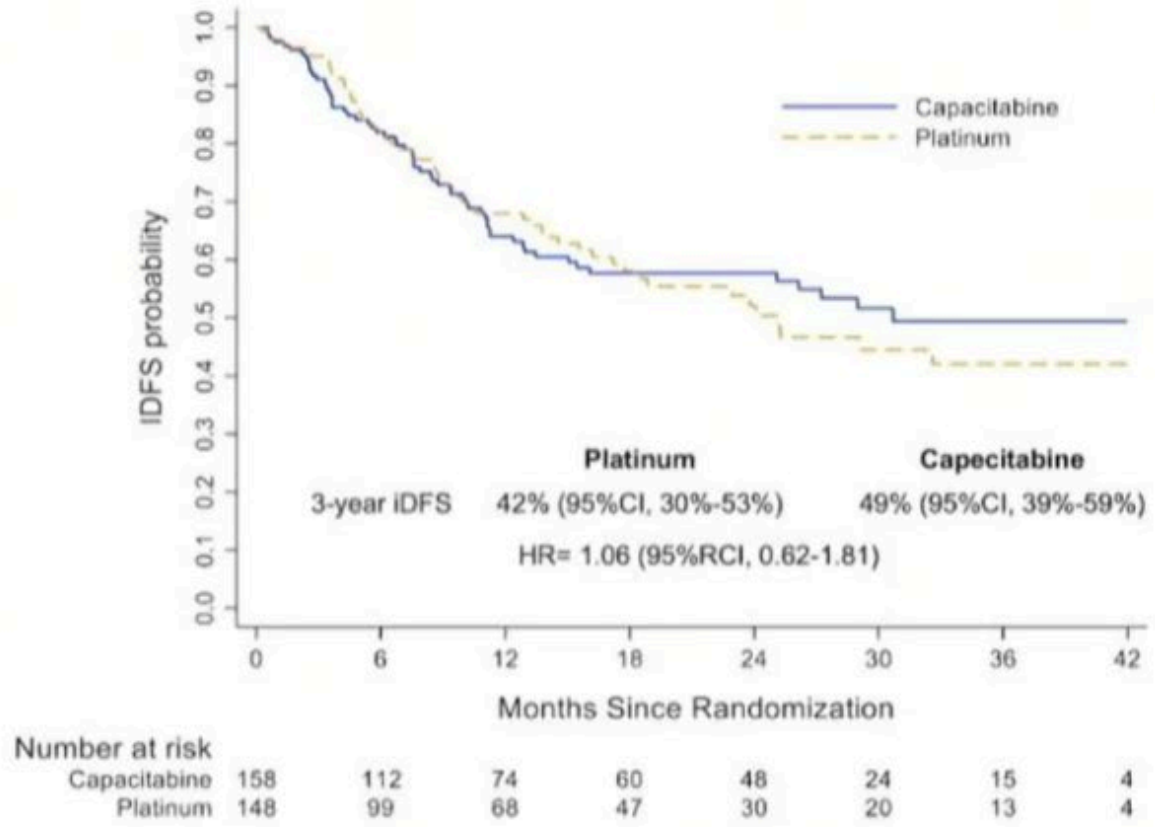
Non-inferiority design with superiority alternative

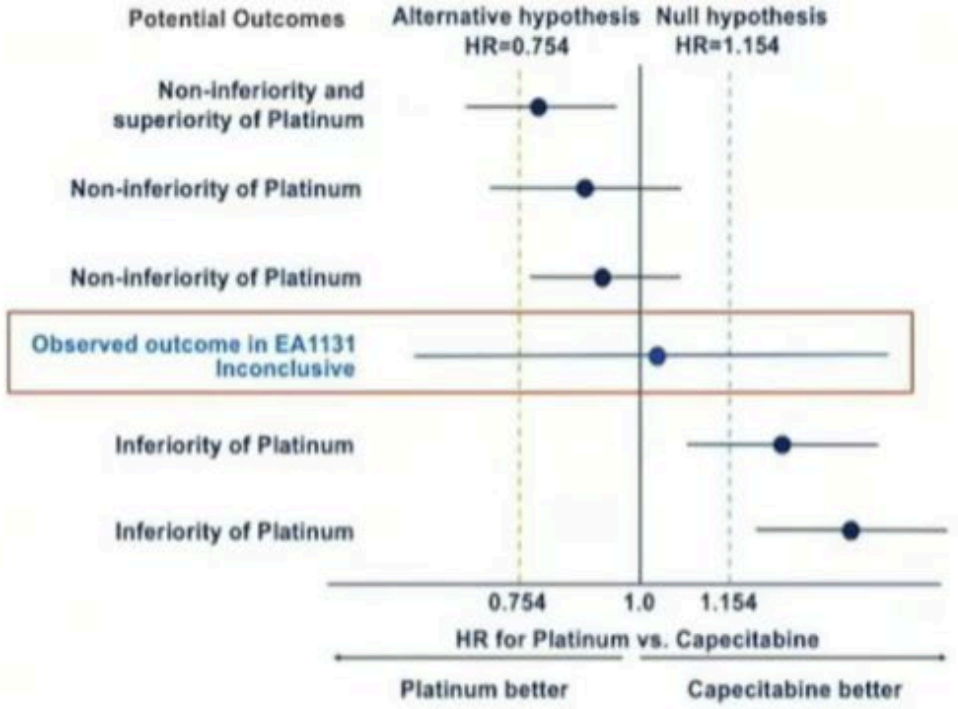
Non-inferiority null hypothesis
- 4-year iDFS 63% platinum vs 67% capecitabine; HR = 1.154

Alternative hypothesis for superiority
- HR = 0.653

Mayer I, et al., ASCO 2021

EA1131: Unable to demonstrate non-inferiority or superiority of platinum





- Trial stopped early for futility
- 308 patients with basal subtype tumors enrolled (78% of total enrollment)
- Median follow-up = 20 months
- 120 iDFS events (of required 196; 61%)

Mayer I, et al., ASCO 2021

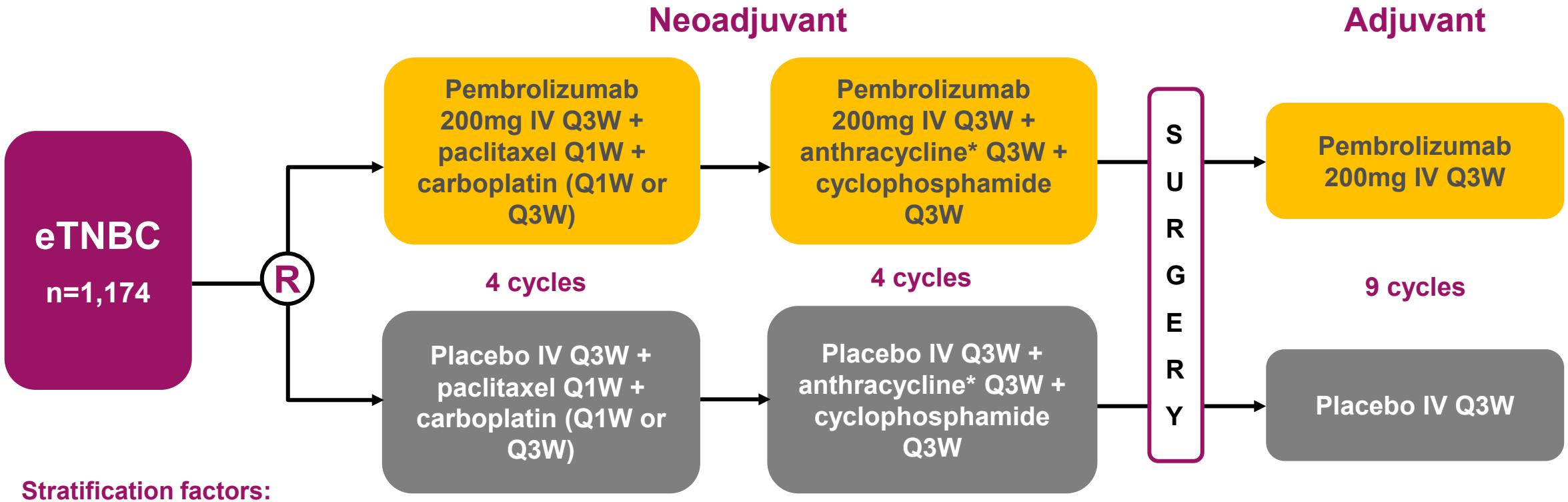
Early-stage TNBC

- Platinum agents
- Immunotherapy
- PARP inhibitors

Randomized TNBC neoadjuvant IO trials

	GeparNUEVO	NeoTRIPaPD-L1	KEYNOTE-522	Impassion 031
Chemotherapy backbone	Nab-paclitaxel -> EC q2 week	Nab-palcitaxel + carbo weekly 2 on/1off x8	Paclitaxel + Carbo -> AX/EC q3 week	Nab-paclitaxel –> AC q2 week
CPI	Anti-PD-L1	Anti-PD-L1	Anti-PD-1	Anti-PD-L1
	± Durvalumab (no adj)	± Atezolizumab (no adj)	± Pembrolizumab 1year	± Atezolizumab 1 year
pCR rate	pCR = 53.4% vs 44.2%	pCR = 43.5% vs 40.8%	pCR = 64.8% vs 51.2%	pCR = 57.8% vs 41.1%
	Δ 9.2% (n=174)	Δ 2.7% (n=280)	Δ 13.6% (n=602)	Δ 16.5% (n=333)
			pCR = 63% vs 55.6%	
			Δ 7.5% (n=1174)	
Primary Endpoint	pCR	EFS	pCR EFS	pCR

KEYNOTE-522: phase III neoadjuvant then adjuvant pembrolizumab study in eTNBC



Stratification factors:

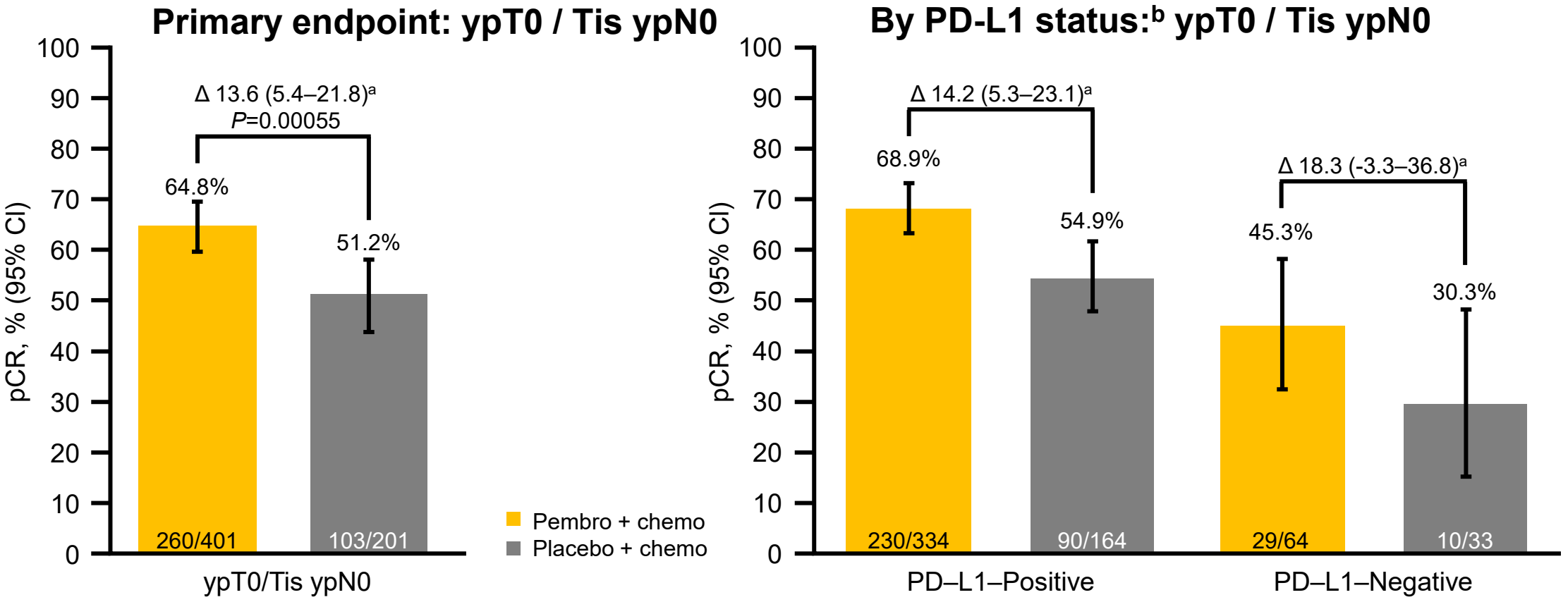
- Nodal status (positive vs negative)
- Tumour size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

Primary endpoints: pCR (ypT0 / Tis ypN0) by local pathologist assessment (ITT), EFS by investigator assessment (ITT)

Secondary endpoints: pCR per alternative definitions (ypT0 ypN0 and ypT0 / Tis) in patients with PD-L1+ tumours, EFS (PD-L1+), OS (PD-L1+ and ITT), tolerability

Key exploratory endpoints: RCB, EFS by pCR, pCR and EFS by TILs

KEYNOTE-522: pCR



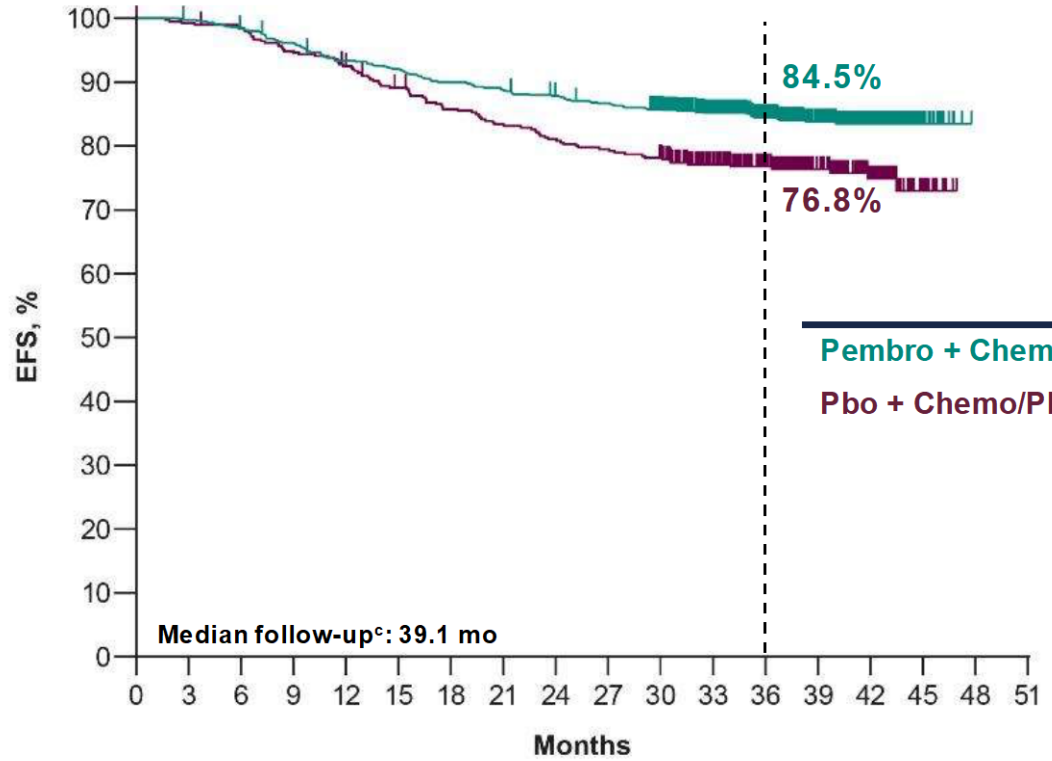
Pembrolizumab showed a statistically significant increase in pCR that was independent of PD-L1 status

[a]Performed after last subject enrolled (data cutoff: 24 September, 2018) based on pre-specified first 602 subjects (pre-calculated boundary for significance: p=0.003); [b]PD-L1 assessed centrally using the PD-L1 IHC 22C3 pharmDx assay and measured by CPS

1. Schmid, et al. ESMO 2019 (Abstract LBA8_PR)

KEYNOTE-522: Event-free survival

Statistically Significant and Clinically Meaningful EFS at IA4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

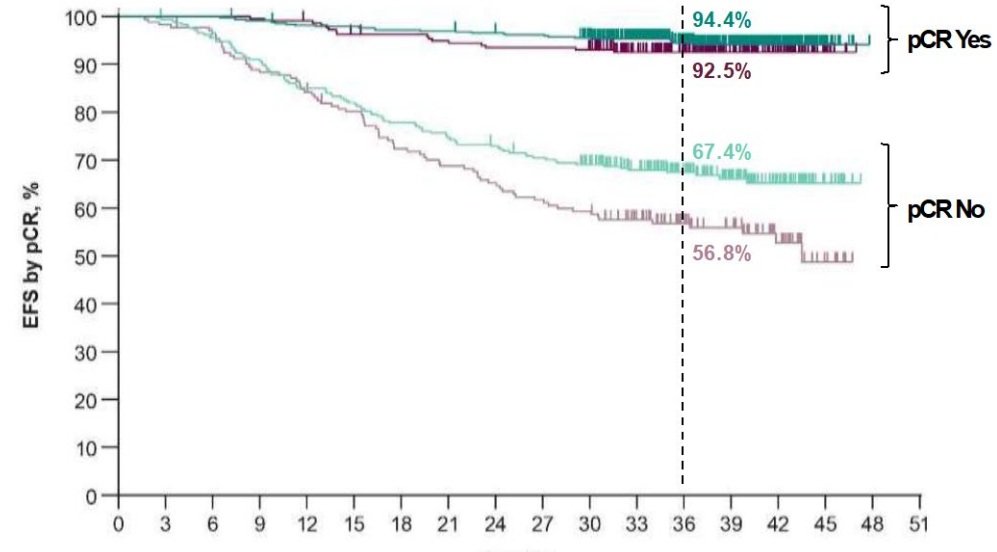
No. at Risk																	
Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Schmid P et al, ESMO Virtual Plenary 2021

KEYNOTE-522: EFS subgroup analysis

EFS by pCR (ypT0/Tis ypN0)

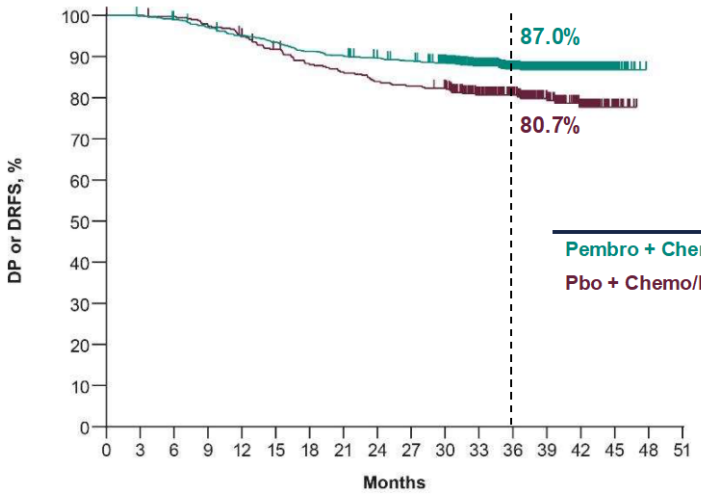


No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Schmid P et al, ESMO Virtual Plenary 2021

KEYNOTE-522: DRFI and OS

Distant Progression- or Distant Recurrence-Free Survival



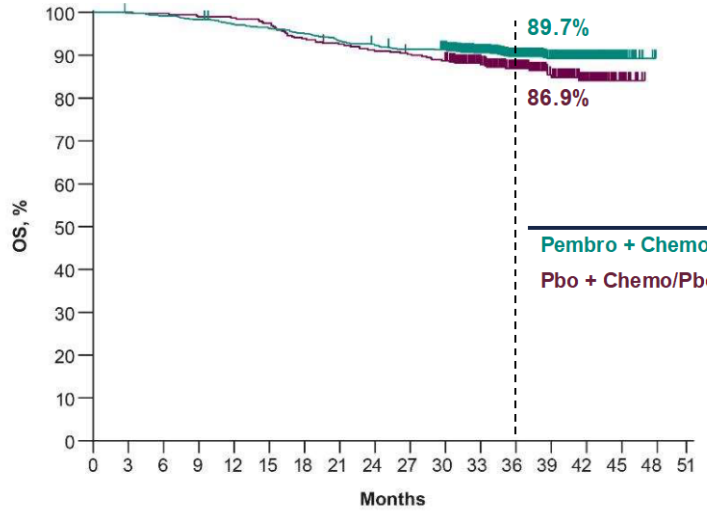
	Events	HR (95% CI)
Pembro + Chemo/Pembro	12.8%	0.61[a] (0.46-0.82)
Pbo + Chemo/Pbo	20.3%	

No. at Risk

Pembro + Chemo/Pembro	784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
Pbo + Chemo/Pbo	390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

Overall Survival



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

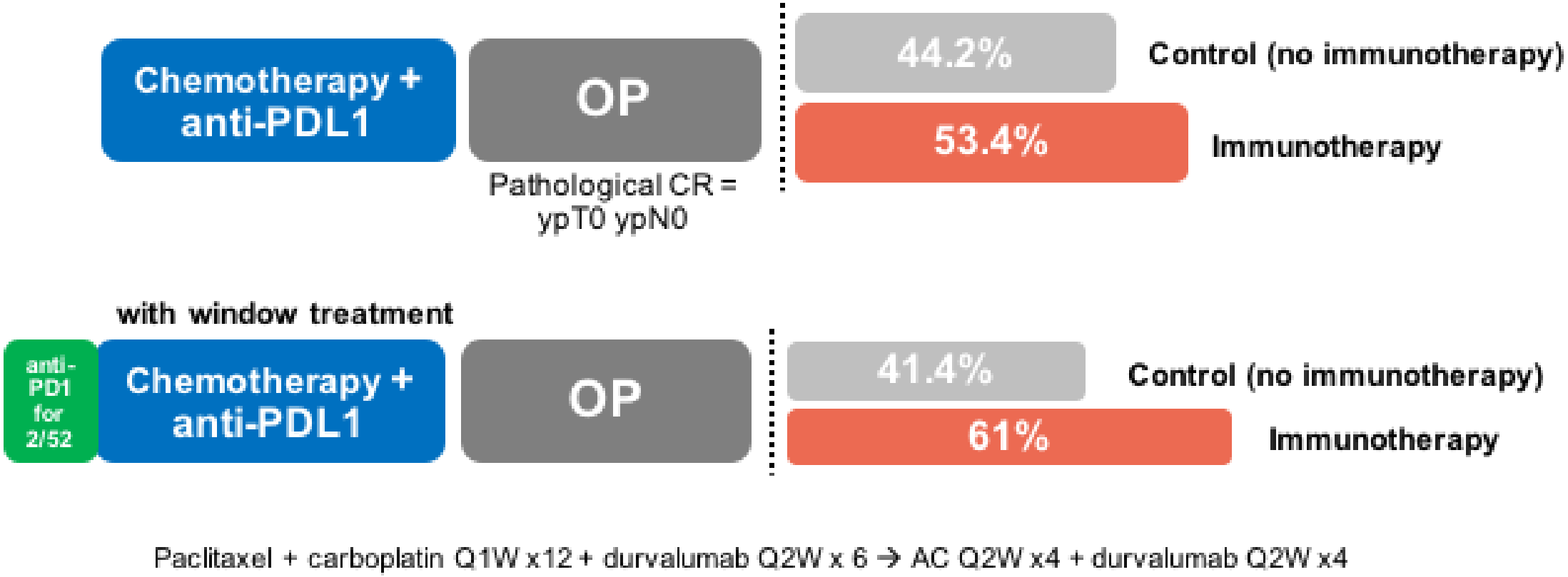
No. at Risk

Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis. Data cutoff date: March 23, 2021.

Schmid P et al, ESMO Virtual Plenary 2021

GepardNuevo Trial: durvalumab in early TNBC



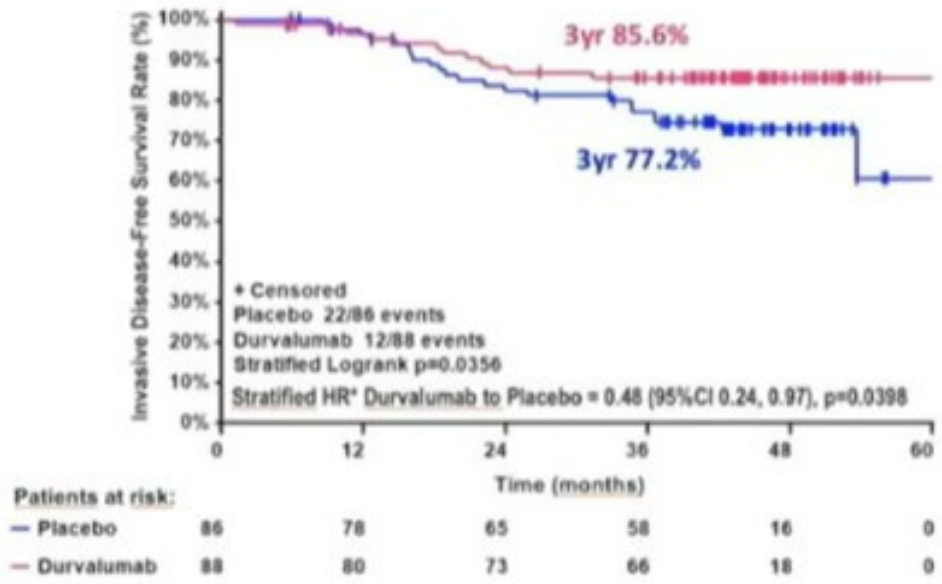
Paclitaxel + carboplatin Q1W x12 + durvalumab Q2W x 6 → AC Q2W x4 + durvalumab Q2W x4

Loibl S *et al.* ASCO 2018.

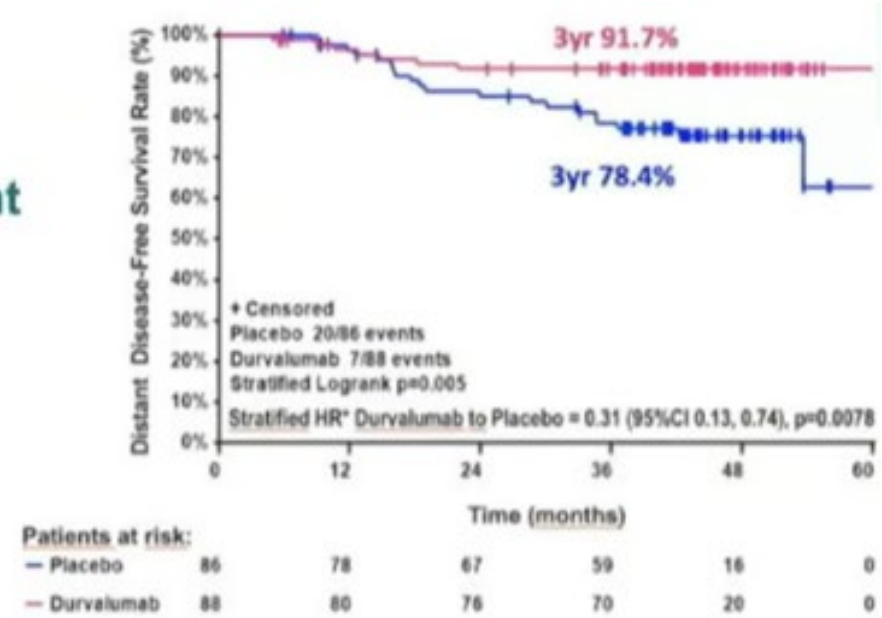
GeparNUEVO: Secondary endpoints

Median follow-up > 3.5 years

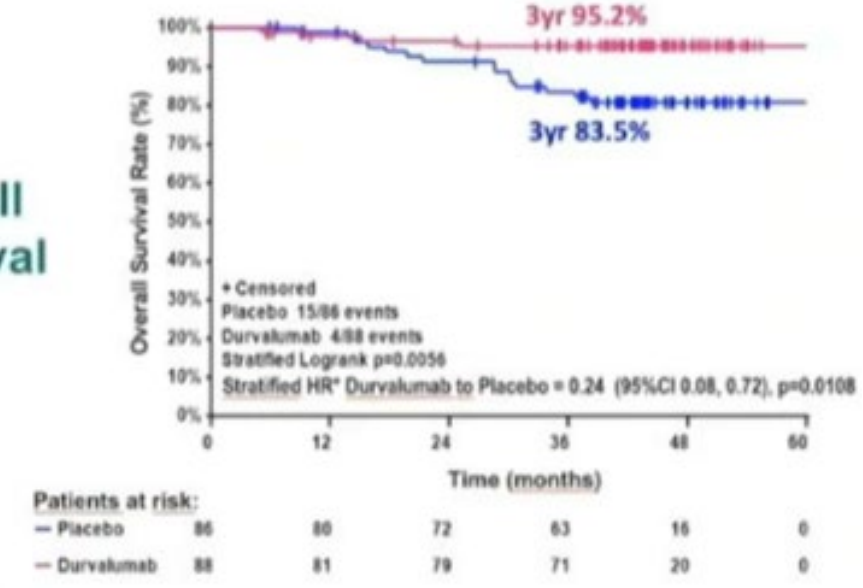
Invasive DFS



Distant DFS



Overall Survival



Loibl S, et al., ASCO 2021

Randomized TNBC neoadjuvant IO trials: Long term outcomes

TRIAL	Regimens	Median FU	Events	HR (95% CI)
GeparNUEVO	Durvalumab+CT vs Placebo+CT	3.5 years	13.6% vs 25.6%	0.48 (0.24-0.97)
KEYNOTE 522	Pembrolizumab+ CT vs placebo+CT	15.5 months	15.7% vs 23.8%	0.63 (0.48-0.82)
Impasssion031	Atezolizumab+CT vs placebo+CT	20.6 months	10.3% vs 13.1%	0.76 (0.4-1.44)

pCR improvement with durvalumab was modest requiring further assessment of association of pCR and longer term outcomes with checkpoints inhibitors

Early-stage TNBC

- Platinum agents
- Immunotherapy
- PARP inhibitors

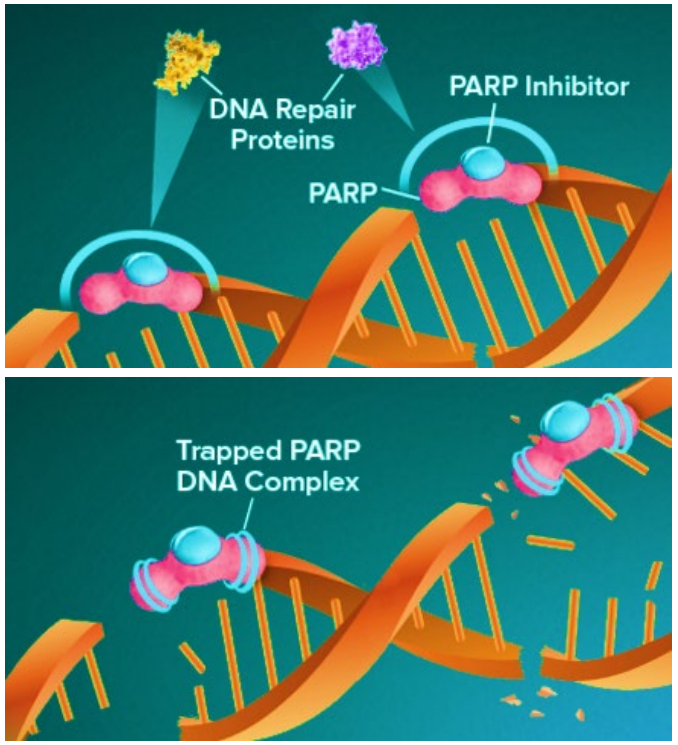
PARP inhibitors in development for Breast Cancer

Potency for catalytic inhibition

Highest

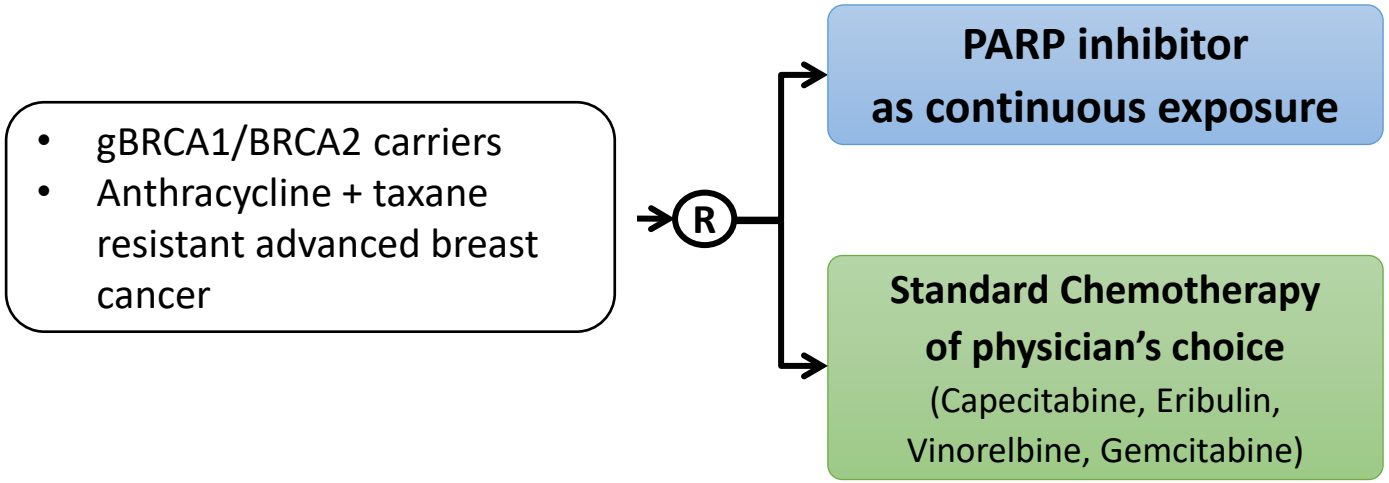
Lowest

Drug Name	PARP Inhibition			Trapping PARP-DNA complex
	PARP1	PARP2	PARP3	
Talazoparib (BMN-673)	■	■		Yes
Niraparib (MK-4827)	■	■		Yes
Rucaparib (AG-14699)	■	■	■	Yes
Olaparib (AZD2281)	■	■	■	Yes
Veliparib (ABT-888)	■	■		No/weak



Single agent PARPi: FDA Registration studies for BRCA1/2 mutated Advanced Breast Cancer Patients

Study Design



Note: Platinum is not included in comparator arm

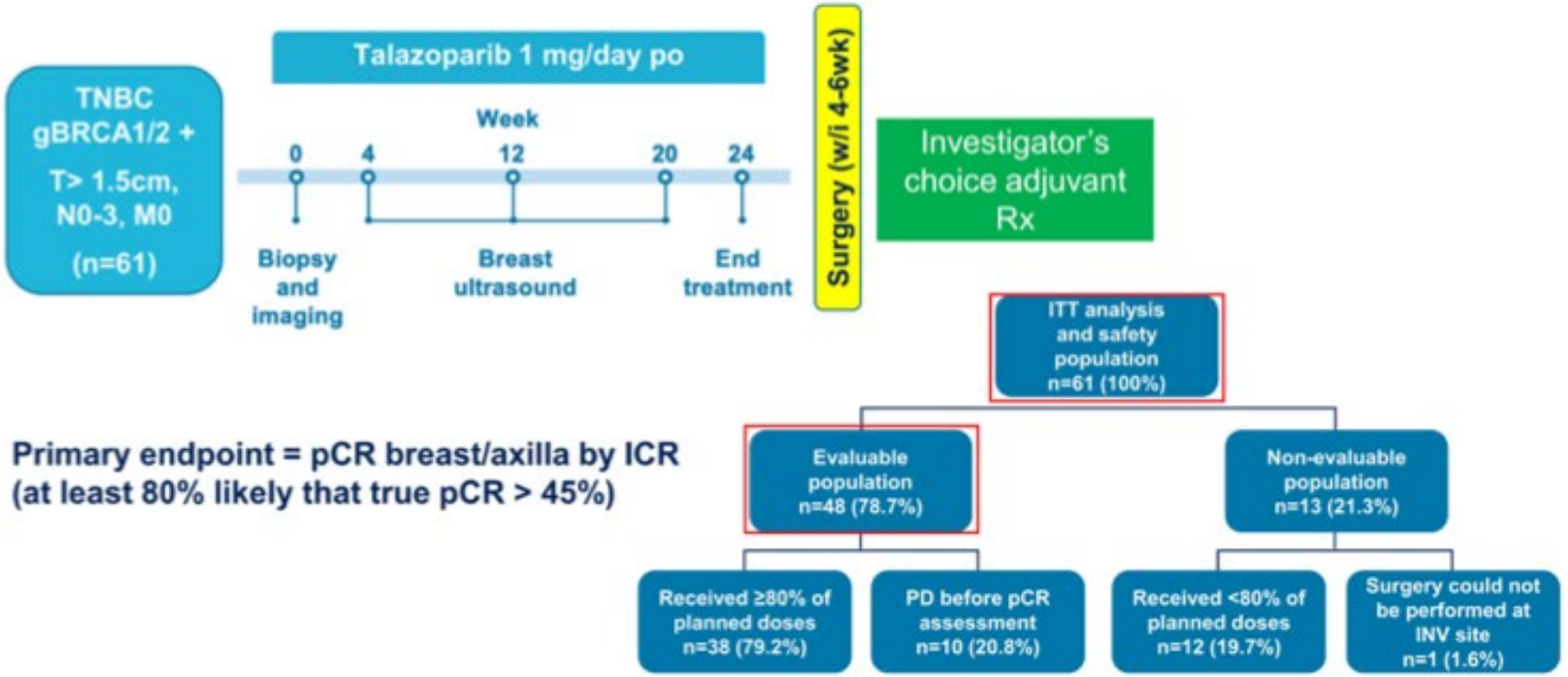
Primary endpoint:

Progression-free survival

PARP inhibitor	Study	NCT number	Status	
Olaparib	**OLYMPIAD**	NCT02000622	completed	Approved by FDA
Talazoparib	**EMBRACA**	NCT 01945775	completed	Approved by FDA

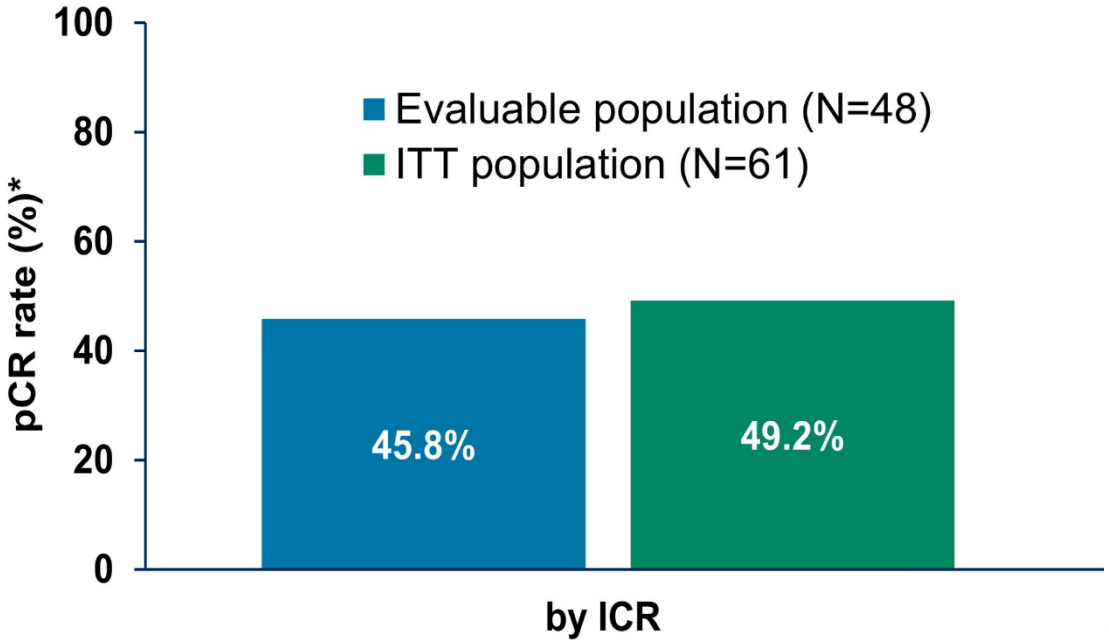
Neoadjuvant Talazoparib for Early Stage Breast Cancer Patients with a BRCA Mutation

NEOTALA: study design



Litton JK, et al., ASCO 2021

NEOTALA: Results



The most common treatment-related adverse events experienced by ≥10% of patients*

	Talazoparib (N=61)				
Number (%) of Patients by Preferred Term*	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Any Adverse Event†	22 (36.1)	9 (14.8)	26 (42.6)	1 (1.6)	58 (95.1)
Fatigue	34 (55.7)	12 (19.7)	1 (1.6)	0	47 (77.0)
Nausea	31 (50.8)	7 (11.5)	1 (1.6)	0	39 (63.9)
Alopecia	33 (54.1)	2 (3.3)	0	0	35 (57.4)
Anemia	4 (6.6)	1 (1.6)	24 (39.3)	0	29 (47.5)
Headache	16 (26.2)	2 (3.3)	1 (1.6)	0	19 (31.1)
Dizziness	11 (18.0)	1 (1.6)	0	0	12 (19.7)
Constipation	9 (14.8)	2 (3.3)	0	0	11 (18.0)
Neutrophil count decreased	1 (1.6)	2 (3.3)	5 (8.2)	1 (1.6)	9 (14.8)
White blood cell count decreased	5 (8.2)	3 (4.9)	1 (1.6)	0	9 (14.8)
Decreased appetite	7 (11.5)	1 (1.6)	0	0	8 (13.1)
Diarrhea	6 (9.8)	2 (3.3)	0	0	8 (13.1)

18.0% (11/61) patients experienced all-causality treatment-emergent SAEs
- Grade 3 anemia was the most common treatment-related SAE (14.8% [9/61]) and reported as a medically important event (which is a known AE of talazoparib)
- No deaths occurred during the reporting period

*In the Safety Analysis Set. Includes all data collected since the first dose of study drug. If the same patient had more than one occurrence in the same preferred term event category, only the occurrence with maximum CTCAE grade is counted. Patients are counted only once per event. MedDRA v23.1 coding dictionary applied. NCI-CTCAE version 4.03.
†As per summary of all TEAEs without ≥10% threshold.

pCR ~ 45%
Single agent PARPi very active in gBRCA+ TNBC, pCR close to polychemotherapy

Talazoparib was generally well tolerated, no unexpected safety findings, AE's were consistent with the established safety profile

Litton JK, et al., ASCO 2021

BIG Breast International Group

frontier science

NRG ONCOLOGY Advancing Research. Improving Lives.

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A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

2021 ASCO ANNUAL MEETING

OlympiA: Trial schema

- Local genetic testing or on-study central screening
  (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

Neoadjuvant Chemotherapy (≥ 6 cycles) → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **Adjuvant Chemotherapy** (≥ 6 cycles) → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

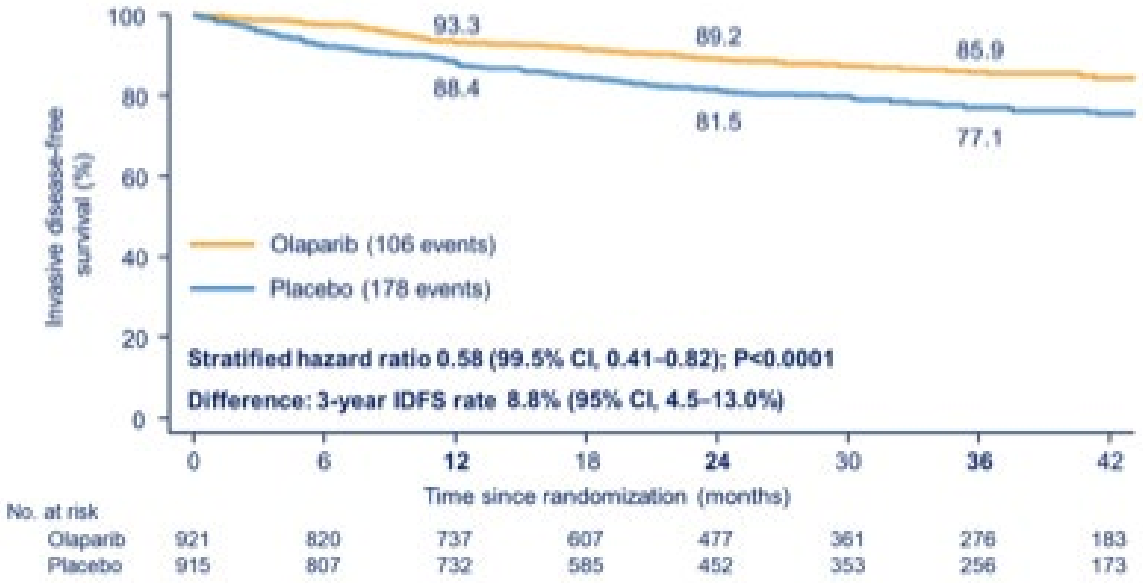
OlympiA: Patient characteristics

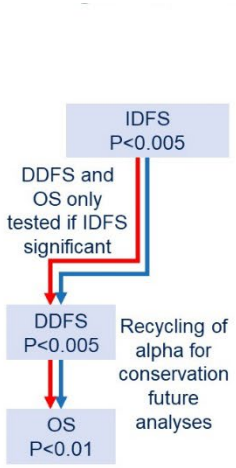
	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

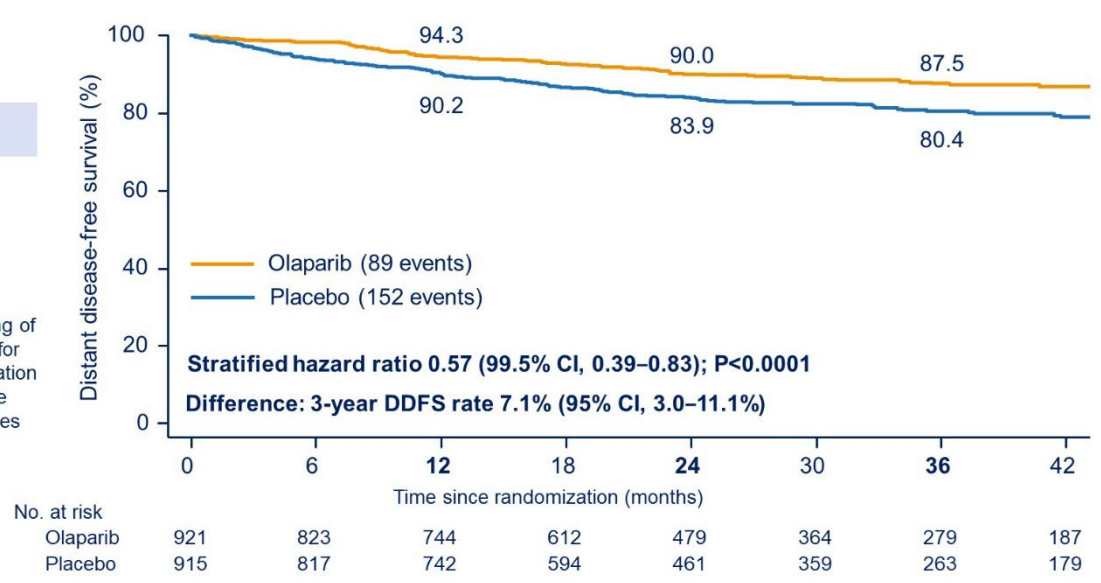
Olaparib in adjuvant gBRCAmut HER2- BC

Invasive disease-free survival (ITT)





Distant disease-free survival



OlympiA: Summary of adverse events

	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	835 (91.7%)	753 (83.3%)
Serious adverse event (SAE)	**79 (8.7%)**	**76 (8.4%)**
Adverse event of special interest	**30 (3.3%)**	**46 (5.1%)**
MDS/AML	**2 (0.2%)**	**3 (0.3%)**
Pneumonitis	9 (1.0%)	11 (1.2%)
New primary malignancy	**20 (2.2%)**	**32 (3.5%)**
Grade ≥ 3 adverse event	221 (24.3%)	102 (11.3%)
Grade 4 adverse event	**17 (1.9%)**	**4 (0.4%)**
Adverse event leading to permanent discontinuation of treatment*	**90 (9.9%)**	**38 (4.2%)**
Adverse event leading to death†	1 (0.1%)	2 (0.2%)

Adjuvant Olaparib in gBRCA+ patients
Considerations:

- **Genetic test**: necessary to make treatment decision, not just to manage future cancer risks
- **Duration**: Is one year the optimal duration of adjuvant olaparib?
- **Safety**: will there be more MSD/AML with longer follow-up
- **Patient selection**: adjuvant PARPi for all subgroups of patients?
- **Comparison/Integration with other treatments**:
  I. HR+/HER2-: abemaciclib
  II. TNBC: capecitabine – immunotherapy - platinum

Early-stage HER2+ breast cancer

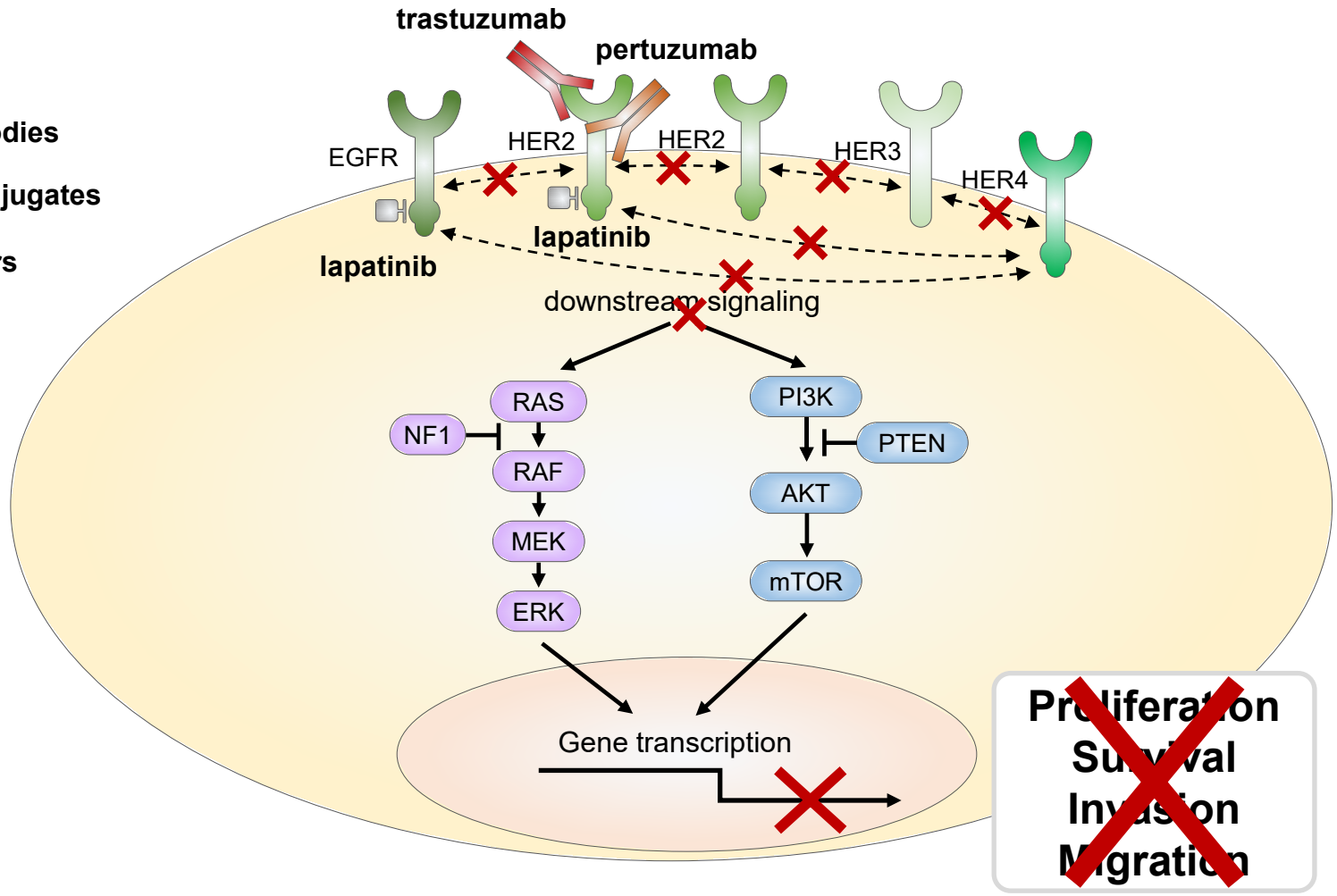
- Dual HER2-blockade
- De-escalation

Dual HER2 targeted therapy improve pCR rates in HER2+ early BC

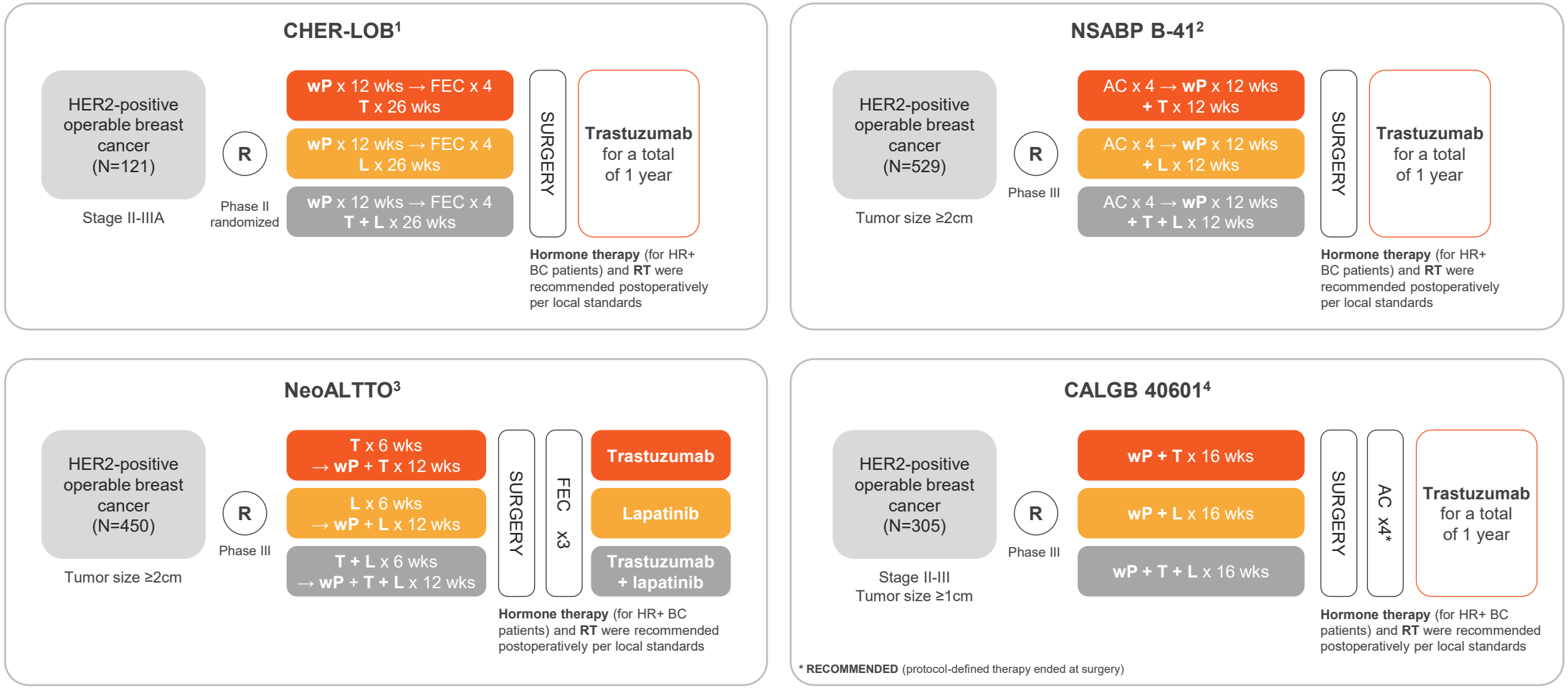
HER2-monoclonal antibodies

HER2-antibody–drug conjugates

Tyrosine-kinase inhibitors



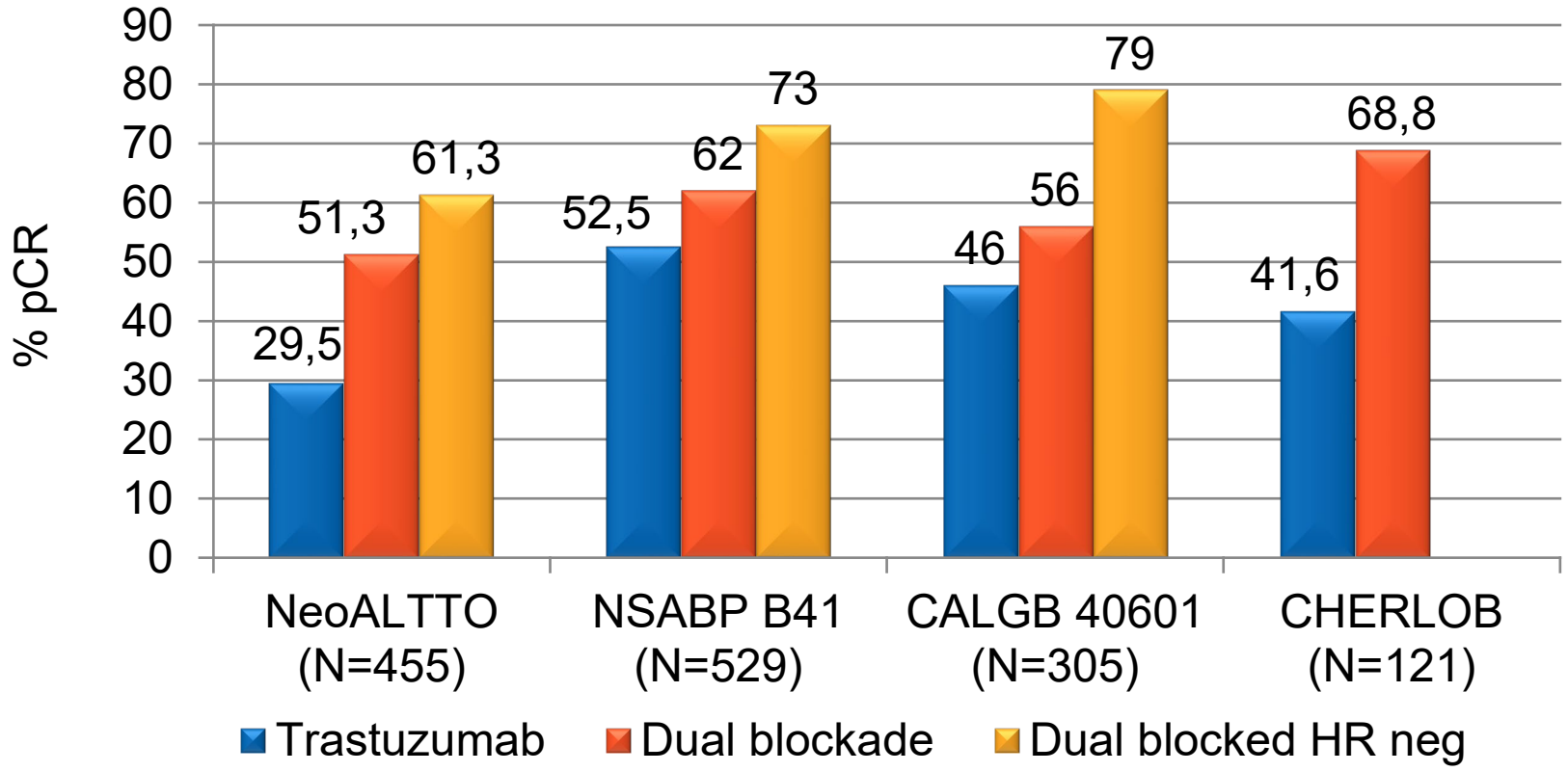
Survival after neoadjuvant therapy with trastuzumab-lapatinib and chemotherapy in patients with HER2-positive early breast cancer: A meta-analysis of randomised trials



T: trastuzumab; wP: weekly paclitaxel; L: lapatinib; RT: radio therapy; AC: anthracycline, cyclophosphamide; FEC: fluorouracil, epirubicin, cyclophosphamide

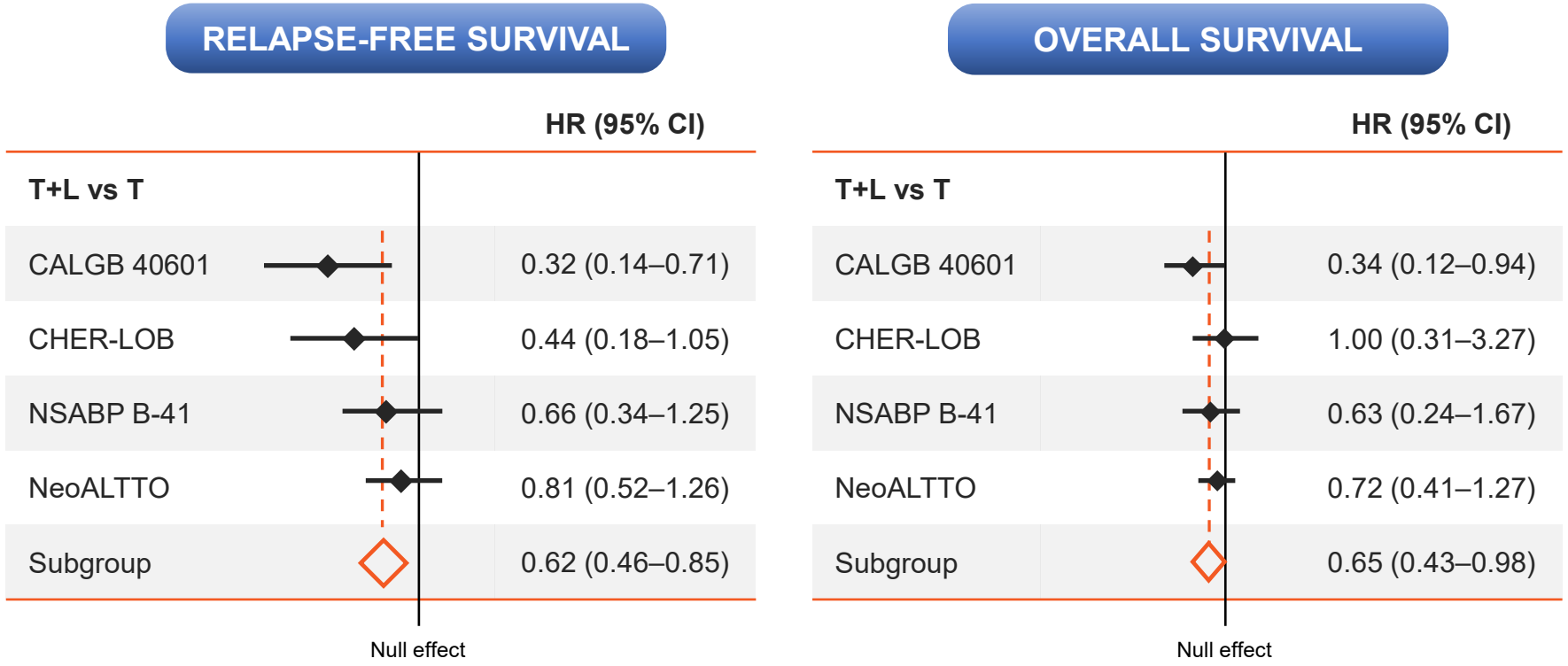
Guarneri V, et al. ESMO 2021

pCR rate with dual blockade in different trials



Baselga J et al, Lancet Oncol, 2012
Robidoux A et al, Lancet Oncol, 2013
Gianni L et al, Lancet Oncol, 2012
Guarneri V et al, J Clin Oncol 2012
Carey LA et al, J Clin Oncol 2016

Relapse-free and overall survival according to lapatinib use (T+L vs T)



CI: confidence interval

Guarneri V, et al. ESMO 2021

Early-stage HER2+ breast cancer

- Dual HER2-blockade
- De-escalation

De-escalated Treatment in HER2+ disease

De-escalation strategies:

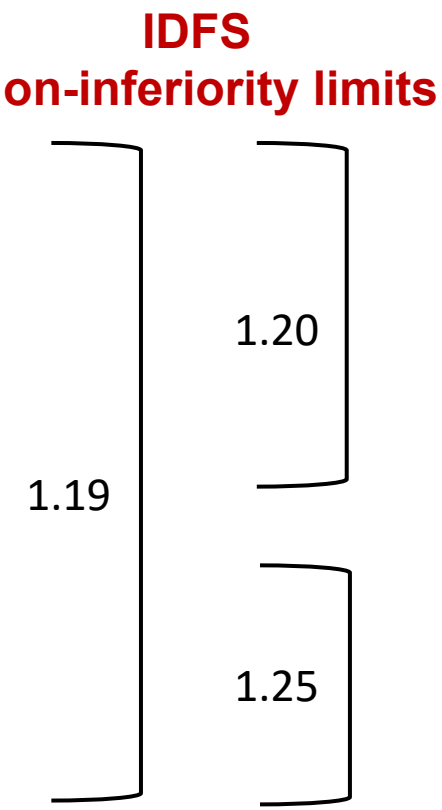
I. Shorter trastuzumab duration

II. Reduction of chemotherapy backbone

III. Chemo-free regimens

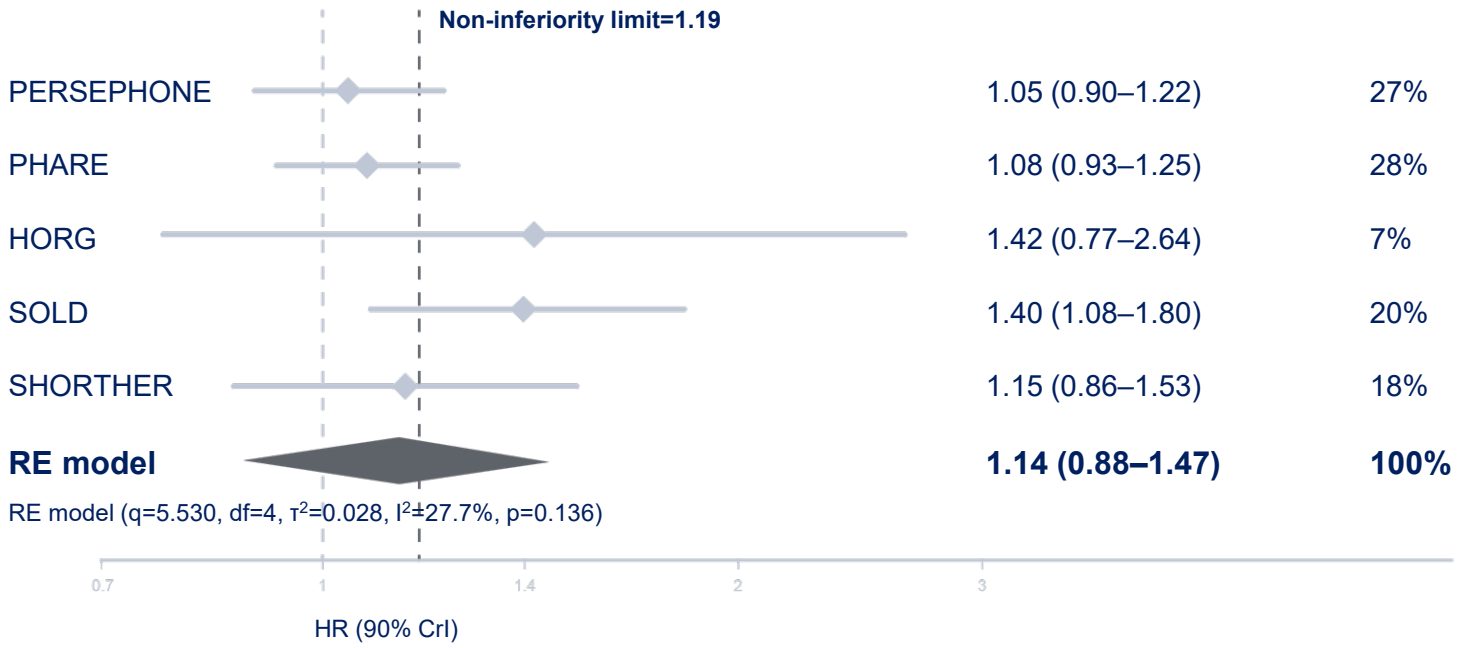
Individual patients data meta-analysis of 5 non-inferiority RCTs of reduced duration single agent adjuvant trastuzumab in the treatment of HER2 positive early breast cancer

	Trial	Duration	Patients
	PERSEPHONE	12m vs 6m	4088
	PHARE	12m vs 6m	3380
	HORG	12m vs 6m	493
	Subtotal		**7961**
SOLD	SOLD	12m vs 9w	2174
	Shorter	12m vs 9w	1254
	Subtotal		**3428**
	TOTAL		**11.389**



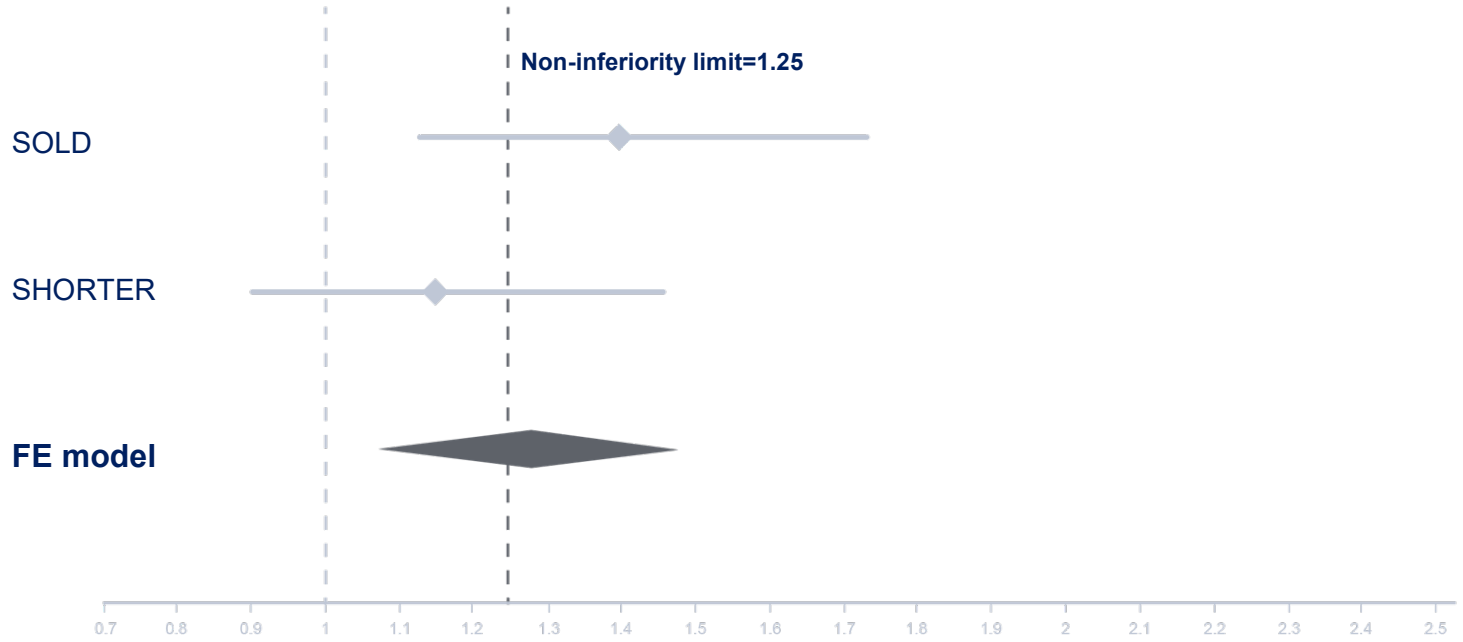
Earl HM, et al. ESMO 2021

Results: 12-month vs shorter (all)



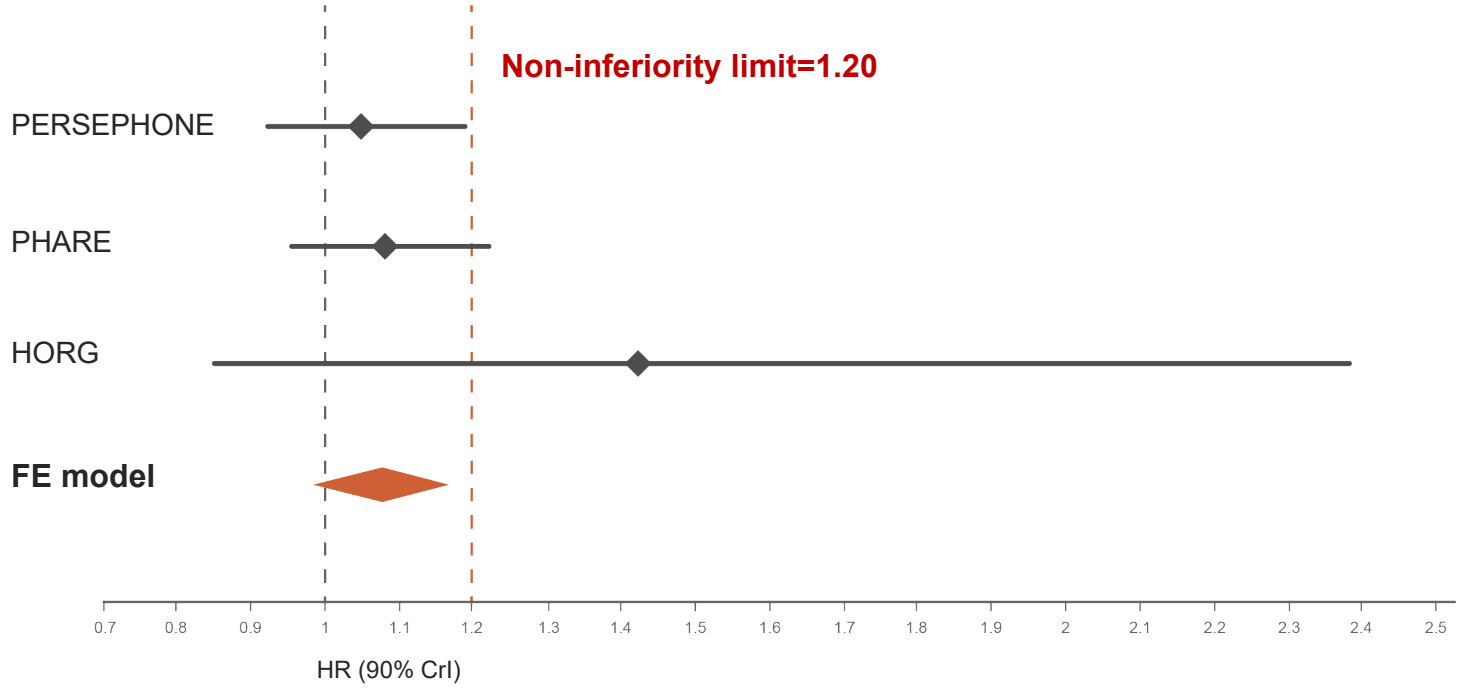
- 5-year IDFS rates were 88.46% and 86.87% respectively.
- The adjusted HR = 1.14 (95% credibility interval (CrI) 0.88–1.47), non-inferiority p=0.37

Results: 12-month vs 9 weeks (2 trials combined – fixed effects model)



- For 12 m vs 9 m, 5-year IDFS rates were 91.40% and 89.22% respectively.
- The adjusted HR for treatment = 1.27 (90% CrI 1.07–1.49), non-inferiority p=0.56

Results: 12-month vs 6-month (3 trials combined – fixed effects model)



- For 12-month vs 6-month, 5-year IDFS rates were 89.26 and 88.56% respectively
- The adjusted HR for treatment was 1.07 (90% CrI 0.98–1.17), non-inferiority p=0.02

CrI: credibility interval; IDFS: invasive disease-free survival; HR: hazard ratio

Earl HM, et al. ESMO 2021

De-escalated Treatment in HER2+ disease

- *De-escalation strategies:*

  1. Shorter trastuzumab duration

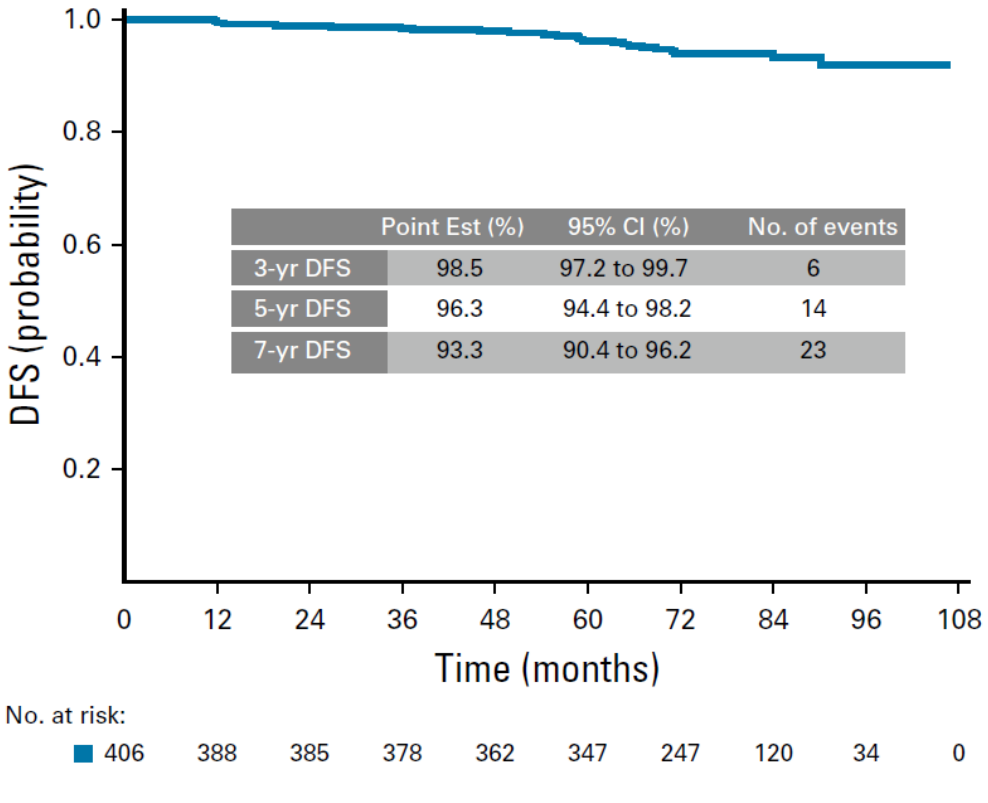
  2. Reduction of chemotherapy backbone

  3. Chemo-free regimens

Adjuvant Paclitaxel and Trastuzumab

Disease-free Survival

All patients

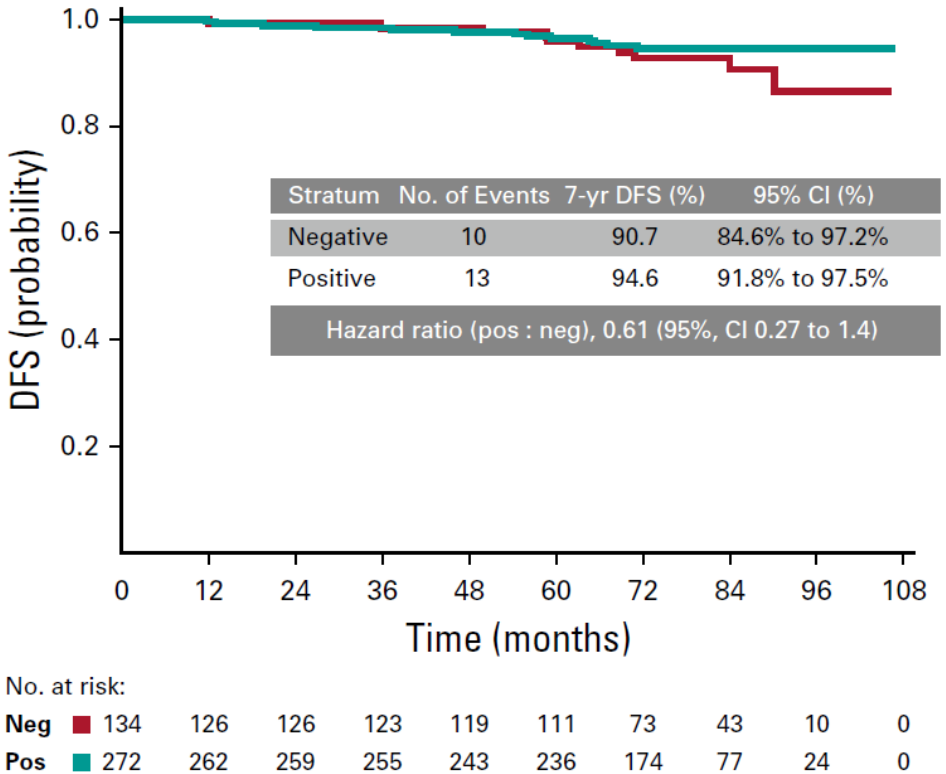


	Point Est (%)	95% CI (%)	No. of events
3-yr DFS	98.5	97.2 to 99.7	6
5-yr DFS	96.3	94.4 to 98.2	14
7-yr DFS	93.3	90.4 to 96.2	23

No. at risk:

■	406	388	385	378	362	347	247	120	34	0

HR+ vs HR-



Stratum	No. of Events	7-yr DFS (%)	95% CI (%)
Negative	10	90.7	84.6% to 97.2%
Positive	13	94.6	91.8% to 97.5%

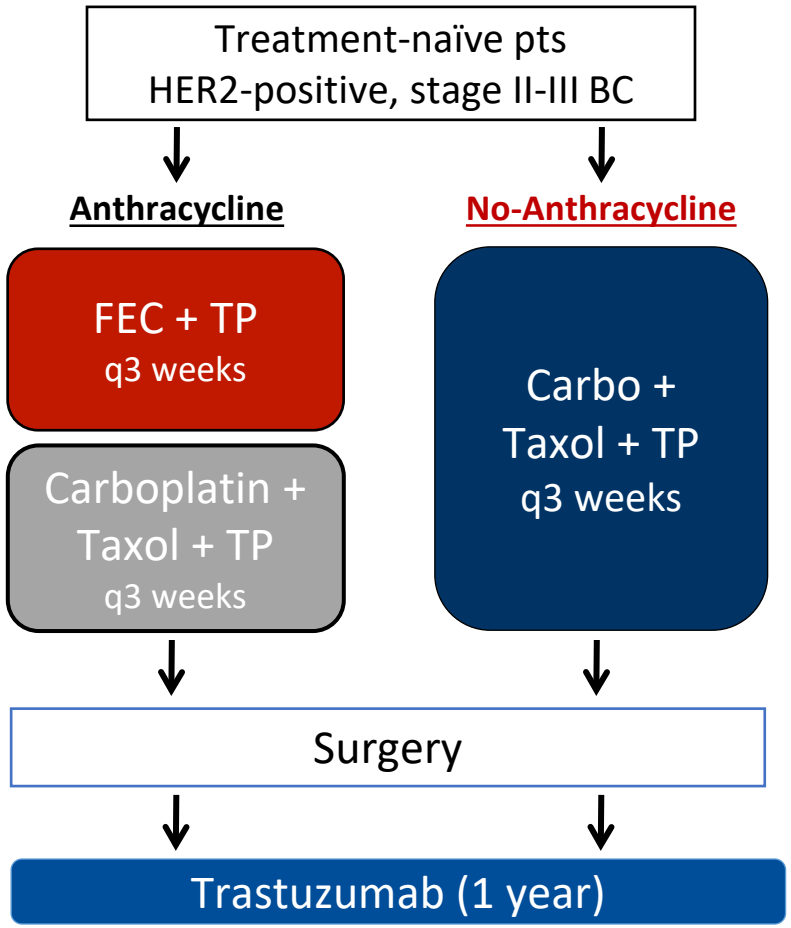
Hazard ratio (pos : neg), 0.61 (95%, CI 0.27 to 1.4)

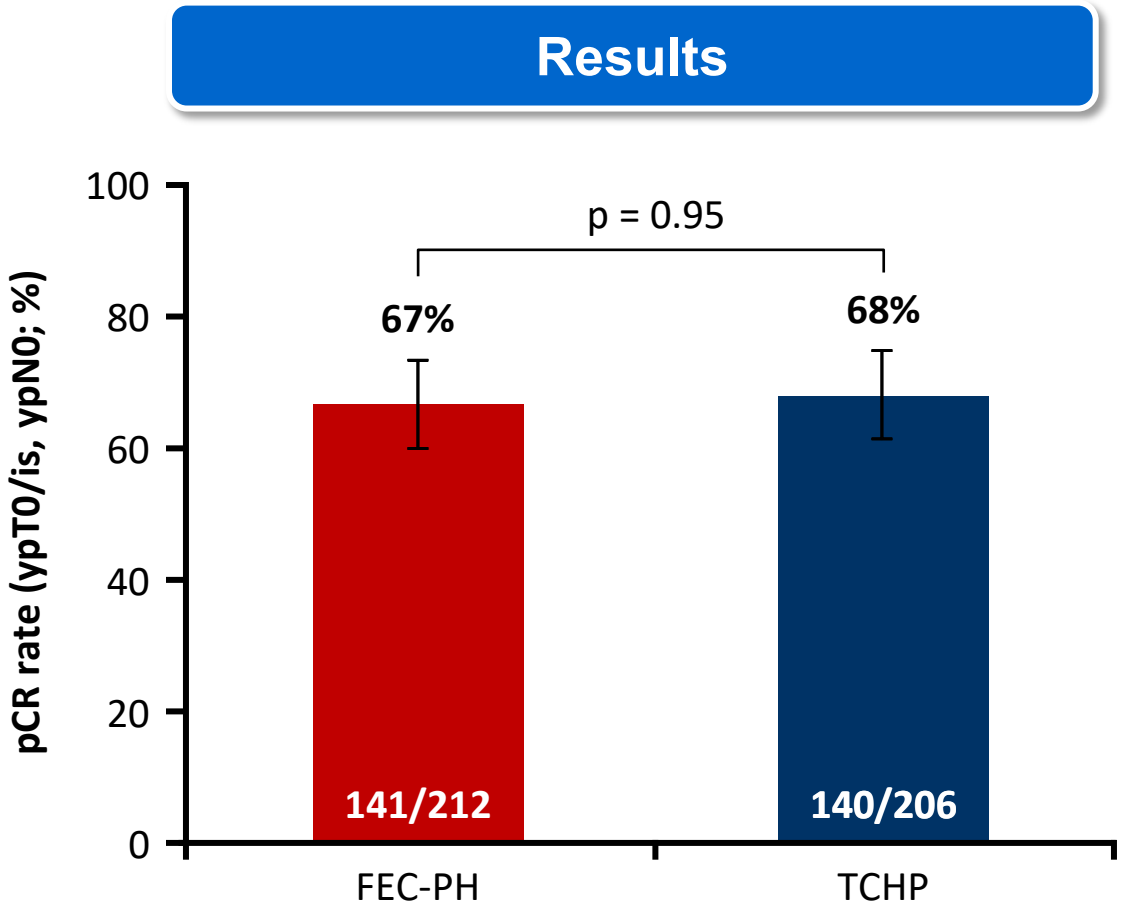
No. at risk:

Neg ■	134	126	126	123	119	111	73	43	10	0
Pos ■	272	262	259	255	243	236	174	77	24	0

Tolaney S et al, JCO 2019

TRAIN-2:
High pCR rates with and without anthracyclines



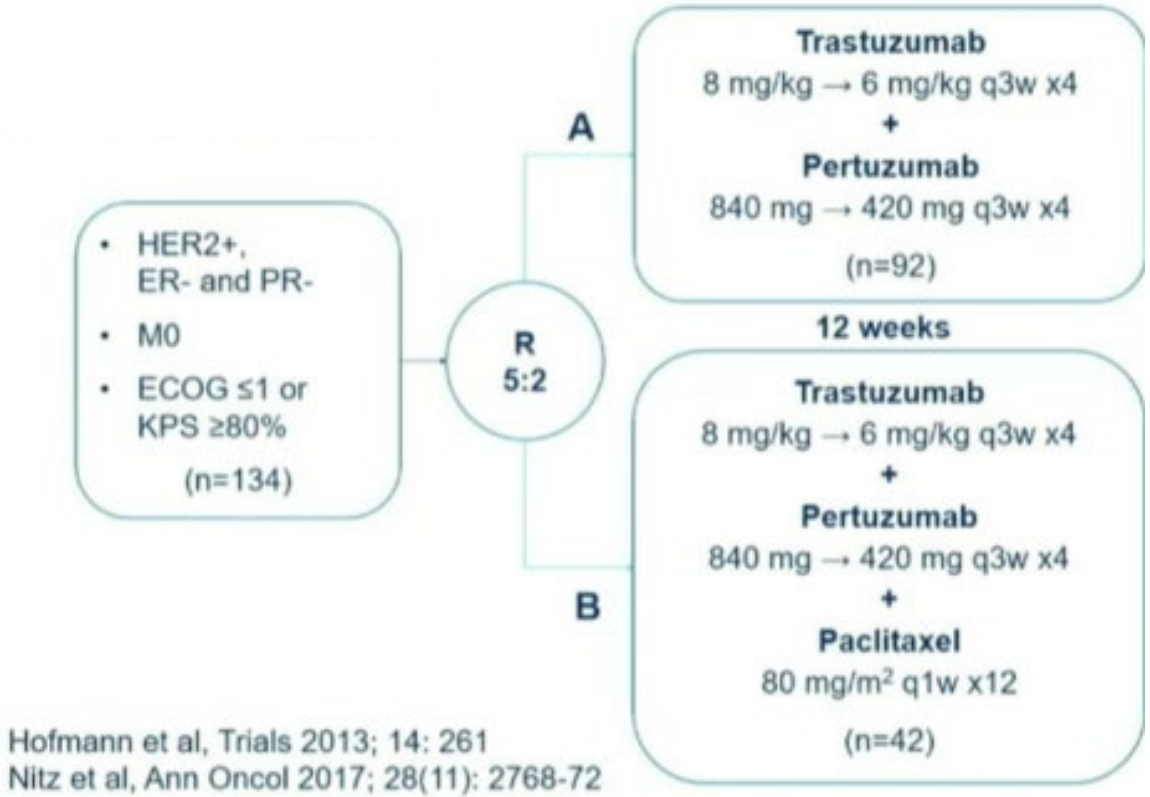


FEC-PH, 5-fluorouracil + epirubicin + cyclophosphamide + pertuzumab–trastuzumab; pCR, pathological complete response; TCHP, paclitaxel + carboplatin + pertuzumab–trastuzumab.

van Ramhorst MS, *et al. Lancet Oncol* 2018.

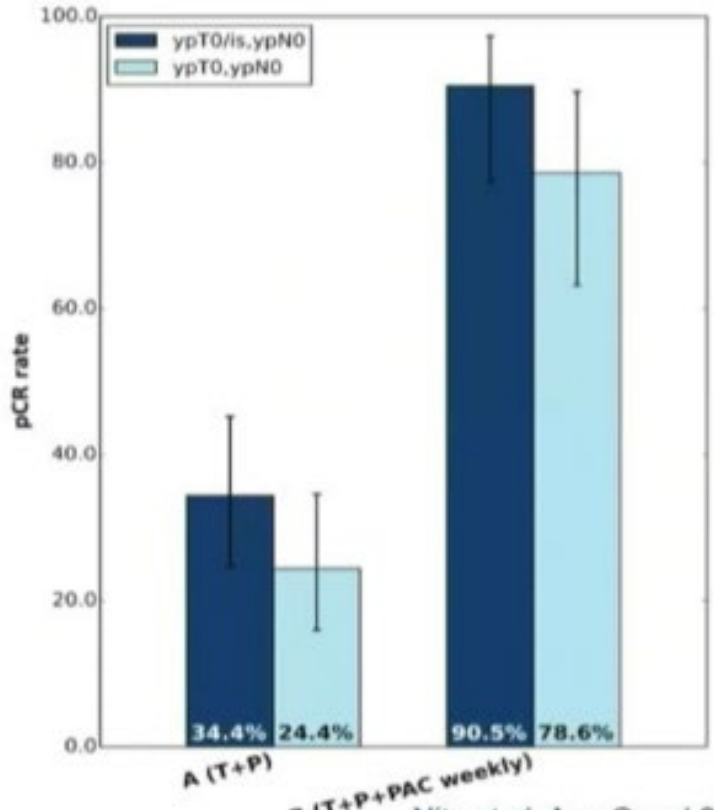
WSG-ADAPT HER2+/HR-

Study Design



Hofmann et al, Trials 2013; 14: 261
Nitz et al, Ann Oncol 2017; 28(11): 2768-72

pCR Rate

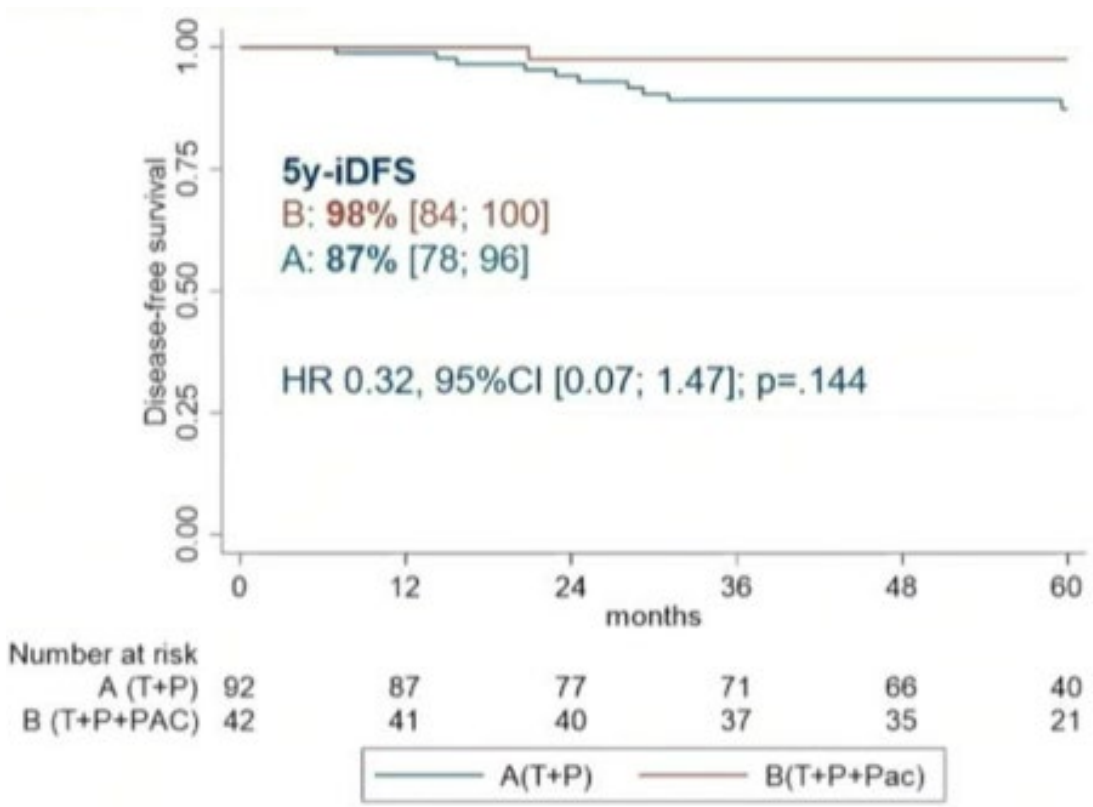


Nitz et al. Ann Oncol 2017: 28(11): 2768-72

Harbeck N, et al., ASCO 2021

WSG-ADAPT HER2+/HR-

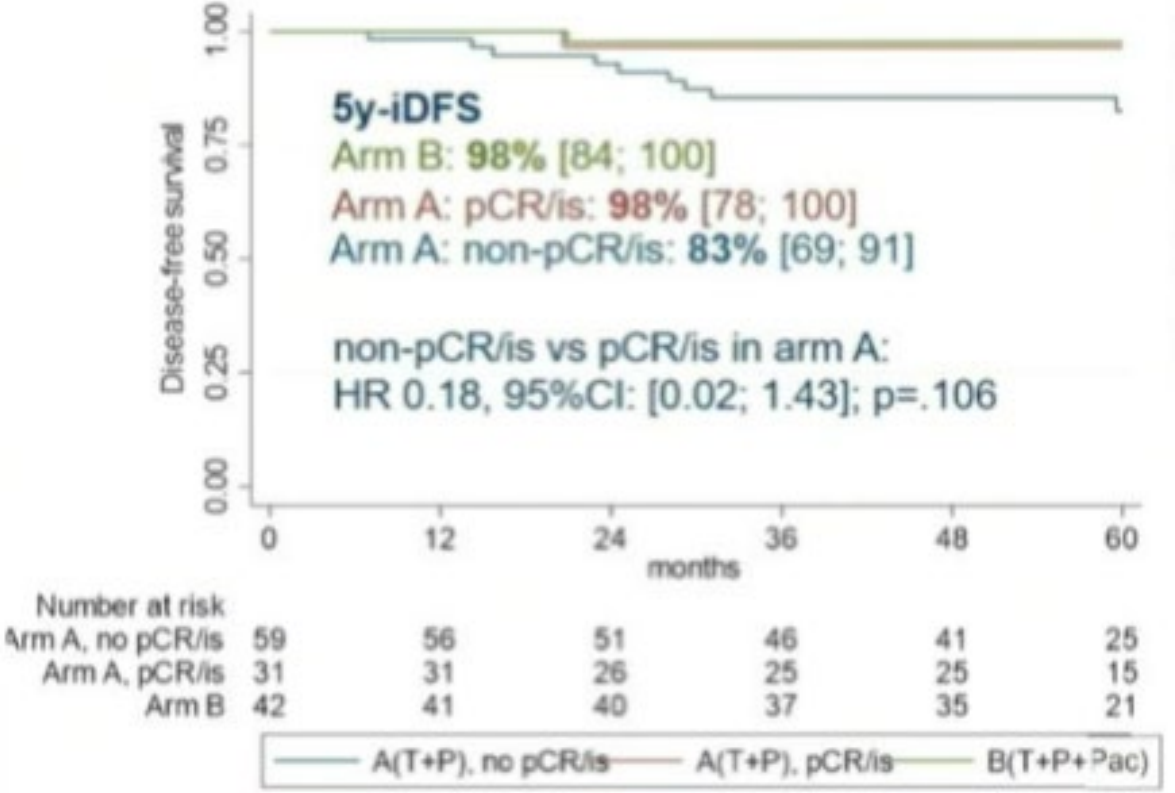
iDFS Arm A: non-pCR vs PCR



Patients with
no further CT after pCR

Arm A	Arm B
9 (29.0%)	30 (79.0%)

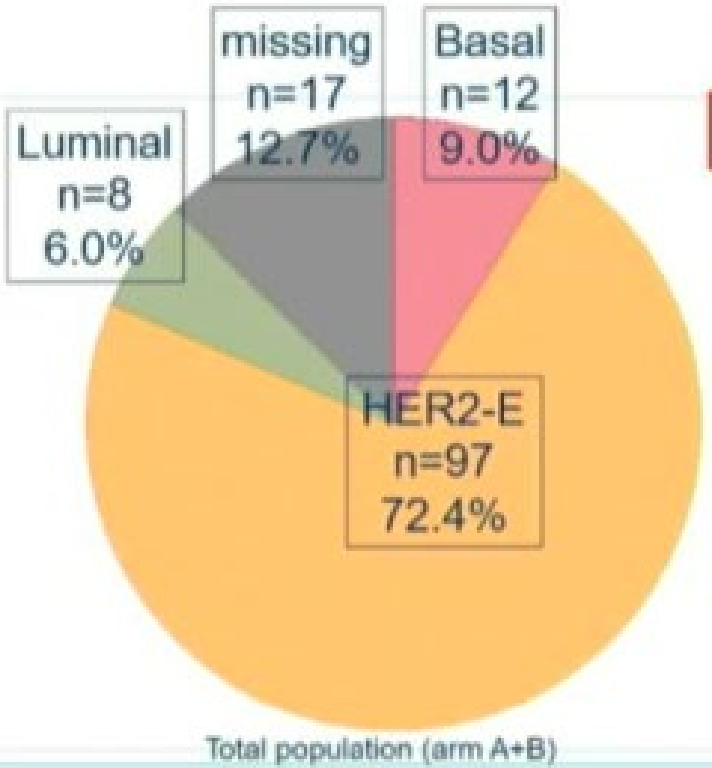
iDFS Arm A: non-pCR vs PCR



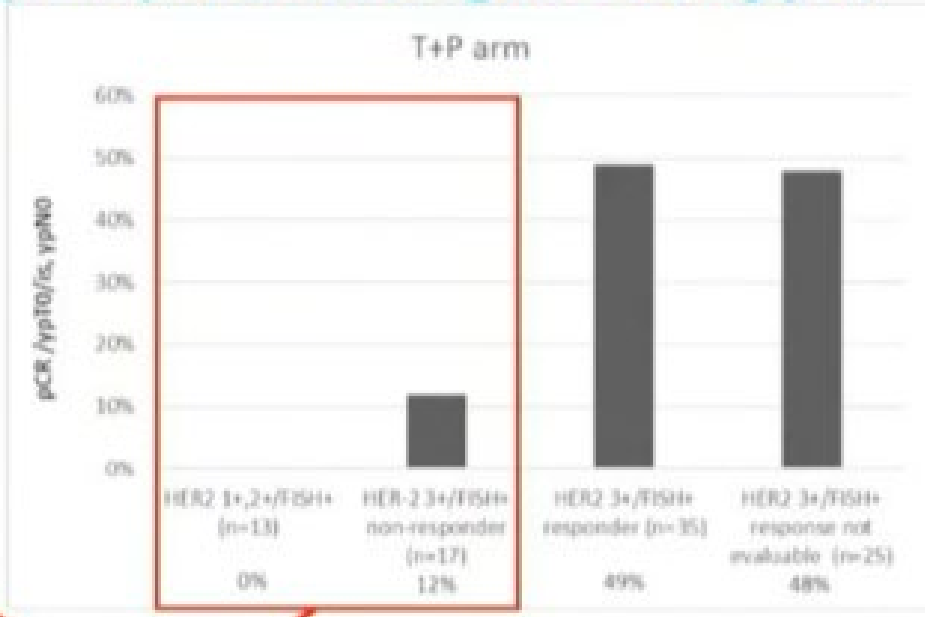
Harbeck N, et al., ASCO 2021

WSG-ADAPT HER2+/HR-

Benefit from neoadjuvant CT-free regimen (T+P) according to subtype, HER2 status by IHC, and early response



pCR rate arm A (T+P)
non-basal: 31/85 (36.5%)
basal: 0/7 (0%)



Gluz et al, SABCS 2019

non-sensitive population: 31/92 (33.7%)

Harbeck N, et al., ASCO 2021

Grazie per l’attenzione